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The feasibility of performing a randomised controlled trial of therapeutic hypothermia for neuroprotection after paediatric cardiac arrest in the UK

by

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A thesis submitted in requirement for the degree of

Doctor of Philosophy (Medicine)

University of Warwick, Medical School,

Division of Health Sciences

August 2012



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Dedication

This thesis is dedicated to my wife, Louise and my children, Beatrice, Chester and Agnes who have patiently and lovingly supported me through this long and emotional journey.

Thank you x.

Acknowledgment

The studies contained within this thesis were generously supported by the paediatric intensive care research department of Birmingham Children's Hospital.

I have been very fortunate to have had the help, guidance and encouragement of many people throughout my period of study at Warwick University and beyond. In particular I would personally like to thank the following:

Dr Kevin Morris	Dr Mark Peters
Dr Heather Duncan	Dr Sainath Raman
Prof Fang Gao-Smith	Ms Felicity Haigh
Prof Gavin Perkins	Dr Peter Fitzmaurice
Dr Paul Davies	Dr Alex Hussey
Ms Jess Gosney	Dr Philip McShane
Ms Victoria Sanders	Dr Roger Parslow
Mr David Scholefield	Prof Robert Tasker
Ms Helen Winmill	Dr Robert Scholefield
Dr Sophie Skellett	Rev Judy Scholefield

Contributions of individuals are detailed in the final section of each individual chapter.

I would like to thank in addition, all the staff at PICANet and the paediatric intensive care and emergency care physicians from across the United Kingdom. Particularly the medical, nursing and clerical staff working on the paediatric intensive care units' of Birmingham Children's Hospital, Alder Hey Children's Hospital and Great Ormond Street Hospital.

Finally, and most importantly, all the babies, children, young adults and families whose often tragic lives have been my inspiration for this long journey and form the foundations for the knowledge presented here.

Declaration and inclusion of previously published work

Chapters two and three have been published prior to submission of this thesis. Chapter five has been presented at the Paediatric Critical Care World Congress in Sydney. This work was not published or presented prior to the beginning of the candidate's period of study for this degree at the University of Warwick.

This thesis is entirely the work of Dr Barnaby Scholefield. Areas of technical assistance from collaborators are noted at the end of each relevant section.

No part of this thesis has been previously submitted for the award of any degree from the University of Warwick or any other university.

Abstract

Cardiac arrest in paediatric patients often results in death or survival with severe brain injury. Therapeutic hypothermia, lowering of core body temperature to 32 to 34°C may reduce injury to the brain in the period after circulation has been restored. This thesis comprises studies related to the feasibility of performing a randomised controlled trial (RCT) of therapeutic hypothermia for neuroprotection after cardiac arrest in the UK.

A systematic Cochrane review of paediatric evidence finds no published RCTs supporting or refuting the use of therapeutic hypothermia after cardiac arrest. Four on-going RCTs are identified which will add to the future evidence base; however, a future UK RCT is recommended.

Additional support for a RCT is demonstrated by two UK surveys of paediatric intensive care and emergency care clinicians. Current UK practice is varied and clinical equipoise exists regarding post cardiac arrest temperature management.

A national, retrospective study of all admissions to paediatric intensive care after out of hospital (OHCA) and in hospital cardiac arrest (IHCA) shows an overall survival of 76 and 50% respectively. Important differences between IHCA and OHCA populations are identified, recommending separation in a RCT. The incidence rate of cardiac arrest admissions to PICU in the UK is too low to recruit to a UK only RCT, after consideration of sample size requirements.

A large, multi-centre, retrospective, observational study of OHCA patients identified multiple factors associated with survival. A survival prediction model, incorporating: pupillary reaction, blood lactate level and duration of cardiac arrest, is described. The model could be used as a tool for stratified randomisation within a RCT.

Finally, therapeutic hypothermia is retrospectively compared with standard, normothermic temperature management after OHCA. In a limited population, no difference in survival is found; however, important information on application, logistics and safety of the intervention are evaluated.

Abbreviations

ACH	Alder Hey Children's Hospital, Liverpool	OHCA	Out of hospital cardiac arrest
BCH	Birmingham Children's Hospital	OR	Odds ratio
CART	Correlation and regression tree	PaCO ₂	Partial pressure of arterial carbon dioxide
CFAM	Cerebral functioning monitoring (amplitude integrated EEG)	PaO ₂	Partial pressure of arterial oxygen
CI	Confidence interval	PEA	Pulseless electrical activity
CPR	Cardiopulmonary resuscitation	PCCMDS	Paediatric critical care minimum dataset
ECLS	Extracorporeal life support	PIC	Paediatric intensive care
ECPR	ECLS-cardiopulmonary resuscitation	PICS-SG	Paediatric intensive care society study group
ED	Emergency department	PICANet	Paediatric intensive care audit Network
EEG	Electroencephalogram	PICU	Paediatric intensive care unit
GOSH	Great Ormond Street Hospital	PIM2	Paediatric Index of mortality 2 score
ICP	Intracranial pressure	RCT	Randomised controlled trial
IHCA	In-hospital cardiac arrest	ROSC	Return of spontaneous circulation
ILCOR	International liaison committee on resuscitation	ST	Standard temperature therapy
IPICA	In-paediatric intensive care unit cardiac arrest	TBI	Traumatic brain injury
IQR	Inter quartile range	TH	Therapeutic hypothermia
kPa	kilopascal	VF	Ventricular fibrillation
MED	Median	vs.	Versus
mmol	millimole	VT	Ventricular tachycardia
NAI	Non-accidental injury		

1 General Introduction

"We're going on a bear hunt,

We're going to catch a big one.

What a beautiful day!

We're not scared"

In: We're going on a bear hunt: Michael Rosen (children's novelist; born 1946)

1.1 INTRODUCTION

The death of an infant or child is always a tragedy. Saving an infant or child whose heart stops beating can be seen as a medical miracle. However, for survivors, the loss of a normal future life and quality existence as a result of neurological injury can be a greater tragedy. The hunt for ways to improve post cardiac arrest care and reduce the burden of suffering in this precious population will be a challenge, but the effects on the patients and families may be immeasurable. This thesis starts that journey; to search, question, investigate, analyse and set the future research path, to establish if the use of simple temperature manipulation (therapeutic hypothermia) in these patients may be the key to improving their chances of a normal life after cardiac arrest.

This first chapter aims to introduce the concept of cardiac arrest in children including the current understanding of the incidence and aetiology of paediatric cardiac arrest followed by the impact of the post cardiac arrest syndrome caused by ischaemia reperfusion injury after initial successful resuscitation, with a focus on neurological injury. An overview of therapeutic hypothermia follows. This is a potentially beneficial therapy that may prevent or attenuate the secondary neurological injury following cardiac arrest. The potential mechanism of action, evidence from animal and human clinical trials and important issues regarding actual delivery of therapeutic hypothermia will be outlined. Finally, the feasibility challenges of undertaking a paediatric critical care randomised controlled trial, which will need to be addressed in this thesis, is considered.

1.2 CARDIAC ARREST

1.2.1 Definition and classification

Knowledge of the accepted definition of cardiac arrest, understanding of the four phases of the disorder and the classification of location of cardiac arrest are fundamental building blocks for paediatric cardiac arrest research. Cardiac arrest (also known as cardiopulmonary arrest) is defined as 'the cessation of cardiac mechanical activity, determined by the inability to palpate a central pulse, unresponsiveness and apnoea' (Zaritsky et al, 1995). However, adaptations to this definition have been made in numerous clinical trials, particularly due to difficulties of confirming absent pulses (Tibballs & Russell, 2009; Eberle et al, 1996), and therefore the 'pragmatic definition' of cardiac arrest requiring chest compressions or cardiopulmonary resuscitation (CPR) for a minimum of duration of one minute was suggested (Nichol et al, 2008a). Cardiopulmonary resuscitation (CPR) is a broad term meaning an attempt to restore spontaneous, effective ventilation and circulation (Zaritsky et al, 1995). CPR can be sub-classified into basic (simple airway manoeuvres, mouth to mouth ventilation and chest compression able to be performed by the lay-public without additional medical equipment) and advanced resuscitation techniques (requiring use of specialist equipment; e.g. endotracheal intubation, intravenous medication or extracorporeal life support) (Zaritsky et al, 1995).

In contrast to adults, cardiac arrest in the paediatric age group (infants and children from birth to their 18th birthday) is often preceded by a respiratory deterioration leading to a hypoxia induced cardiac arrest, although primary cardiac disease and ventricular arrhythmias can occur in up to 14% of paediatric cases (Nadkarni et al, 2006). Cardiac arrest and subsequent resuscitation consists of four phases: 1) pre-arrest phase (prevention stage and preceding medical state), 2) no-flow 'arrest' (period of cardiac arrest prior to starting CPR, 3) low flow 'resuscitation' (whilst CPR is in progress) and 4) post resuscitation phase (period from minutes to days after achieving return of spontaneous circulation) (Berg et al, 2008). The effect of each phase with regards duration, management and resistance to treatment for each individual patient is important and affects chances of a sustained return of a spontaneous circulation (ROSC) and subsequent outcome.

Categorising the location of cardiac arrest appears to be important. For example, out of hospital cardiac arrest (OHCA), occurring outside of health care facilities, are less frequently witnessed leading to a more prolonged no-flow phase compared with in-hospital cardiac arrest (IHCA). Other differences between OHCA and IHCA include differences in aetiologies precipitating the cardiac arrest and potential identification of deterioration sooner for IHCA owing to physiological monitoring allowing resuscitation to be started earlier. Within the IHCA group, arrests occurring in a critical care environment, versus standard ward area, may also differ owing to variability in continuous physiological monitoring, adjunctive therapies such as mechanical ventilation and the severity of underlying medical or surgical conditions.

Each individual patient's cardiac arrest will be unique. Multiple factors related to the cardiac arrest may be present or absent to varying degrees (e.g. location of arrest, duration of arrest, cause of arrest and delay and variation in treatment). This variability can lead to significant heterogeneity in studies when patients are combined. To help identify and control for these variables, paediatric 'Utstein' resuscitation definitions and templates for reporting of events surrounding cardiac arrest have been recommended (Zaritsky et al, 1995). Carefully outlining cardiac arrest and resuscitation definitions, whilst standardising with recommended Utstein definitions, will hopefully improve the overall quality of individual studies. In addition, this will allow more useful comparison (and where possible, combination) with other published studies to the benefit of the wider critical care community.

1.2.2 Incidence of cardiac arrest and outcome

So how common is paediatric cardiac arrest in the UK and how serious is the problem? Incidence of paediatric OHCA in the United States of America (USA) is 8 per 100,000 person-years (Atkins et al, 2009) with infants (less than 1 year) having a nine fold increase (72 per 100,000 person-years). This is similar to a smaller study from Helsinki where all cause OHCA rates were 9.8 per 100,000 person-years (Kuisma et al, 1995) and a more recent Japanese OHCA registry study reporting 7.3 per 100,000 person-years (Nitta et al, 2011). However, a study in Melbourne reported an incidence of only 5 per 100,000 person-years for the same age range (Deasy et al, 2010). Unfortunately, UK population OHCA

incidence rates are currently not known and may also vary owing to differences in age, population, race and emergency medical provision hence the search for UK specific data is justified.

Survival and outcome data also vary widely in the reported literature. Table 1-1, Table 1-2 and Table 1-3 outline the main OHCA and IHCA studies published over the last 18 years. Most observational studies and data registries are based on patients in the USA after IHCA or small, often single centre, observational studies after OHCA. The patient population of interest, with respect to post cardiac arrest neuroprotection research, are those successfully resuscitated after cardiac arrest but still at risk of neurological morbidity and death. This is often as a consequence of the original cardiac arrest, hypoxic ischaemic injury and resultant post-cardiac arrest syndrome (Nolan et al, 2008). Many published studies include all cardiac arrest victims and only a small proportion of patients with a return of spontaneous circulation (ROSC). Survival and good neurological outcome rates also vary because of different definitions for cardiac arrest, inclusion of varying patient populations (e.g. sudden infant death syndrome or traumatic arrests), and variable outcome measurements or follow up duration. Traumatic cardiac arrests in particular have traditionally been associated with poorer outcomes. Table 1-1 and Table 1-2 have therefore separated (where possible) the OHCA studies including and excluding traumatic cardiac arrest patients to allow comparison.

Patients suffering OHCA reportedly have a lower survival rate to hospital discharge (8 to 12%) (Young & Seidel, 1999; Donoghue et al, 2005) compared to IHCA (24 to 28%) (Young & Seidel, 1999; Nadkarni et al, 2006; Meaney et al, 2006), when all cardiac arrest victims are included. The proportion of patients achieving ROSC after OHCA is approximately 20 to 30% and after IHCA, 50 to 70%, although the published ranges, again vary considerably (OHCA: 5 to 47%, IHCA 50 to 82%) (Tables 1-1, 1-2 & 1-3). Moler et al (2009) published the only large, observational study reporting outcomes for patients after OHCA and IHCA who achieved a sustained ROSC greater than 20 minutes and were admitted to a paediatric intensive care unit (PICU). Survival rates to hospital discharge and favourable neurological rates were 38% and 49% respectively for OHCA and 49% and 77% for IHCA. However,

extracting the survival rates for patients achieving ROSC in the other cardiac arrest studies produces similarly wide and unreliable variation (OHCA: 14 to 62%, IHCA: 25 to 58%).

Table 1-1 OHCA studies (all causes excluding trauma if possible), number of patients and outcomes

Study	Setting	Study Design	Country	No. of paediatric patients	ROSC (%)	Survival to discharge ^a		Favourable neurology ^b % survivor
						% All	% ROSC	
Donoghue et al (2005)	All	Systematic Review	All	5363	31	12	nr	33
Donoghue et al (2005)	Excluding trauma	Systematic Review	All	3752	23	7	n/a	33
Young and Siedel (1999) ^c	All	Systematic Review	All	1568	nr	8	nr	nr
Nitta et al (2011)	Excluding trauma	Prospective observational	Japan	740	25	7	30	37
Deasy et al (2010)	All	Prospective observational	Australia	209	23	7	29	79
Atkins et al (2009)	All	Prospective observational	USA	624	nr	6	nr	nr
Moler et al (2009) ^d	ROSC > 20mins	Retrospective	USA	138	100	nr	38	49
Herlitz et al (2007)	All	Prospective observational	Sweden	702	nr	6	nr	nr
Ong et al (2006)	All	Retrospective	Canada	474	8	2	23	nr
Lopez-Herce et al (2005)	All	Prospective observational	Spain	95	47	26	56	nr
Young et al (2004)	All	Prospective observational	USA	594	29	9	30	53
Engdahl et al (2003)	All	Prospective observational	Sweden	98	18	5	28	60
Sirbaugh (1999)	All	Prospective observational	USA	300	11	2	18	17
Suominen et al (1997)	All	Retrospective	Finland	50	26	16	62	75
Schindler et al (1996)	All	Retrospective	Canada	80	54	8	14	0
Dieckmann and Vardis (1995)	All	Retrospective	USA	65	5	3	67	50
Kuisma et al (1995)	All	Retrospective	Finland	34	29	15	50	80
Mogayzel et al (1995)	Excluding SIDS	Retrospective	USA	157	27	10	36	47
Hassan et al (1997)	All	Retrospective	UK	43	35	12	33	80

nr: not reported, n/a: not applicable, ROSC: return of spontaneous output. ^a hospital discharge or first available outcome (e.g. one month). ^b author defined favourable neurology. ^c favourable neurology only available from one study in review by Young and Seidel (1999) (28/68 patients). ^d data also published in Moler et al (2011).

Table 1-2 OHCA studies (traumatic arrests only), number of patients and outcomes

Study	Setting	Study Design	Country	No. of paediatric patients	ROSC (%)	Survival to discharge ^a		Favourable neurology ^b % survivor
						% All	% ROSC	
Donoghue (2005)	Traumatic arrest only	Systematic Review	All	1830	nr	401	22	31
Nitta et al (2011)	Traumatic arrest only	Prospective Observational	Japan	135	25	1	1	100
Crewdson et al (2007)	Traumatic arrest only	Retrospective	UK	80	nr	7	9	nr
Calkins et al (2002)	Traumatic arrest only	National trauma registry	USA	25	nr	2	8	nr
Perron et al (2001)	Traumatic arrest only	National trauma registry	USA	729	nr	165	23	nr
Li et al (1999)	Traumatic arrest only	National trauma registry	USA	957	nr	225	20	33

nr: not reported, ^a hospital discharge or first available outcome (e.g. one month). ^b author defined favourable neurology

Table 1-3 IHCA studies, number of patients and outcomes

Study	Setting	Study Design	Country	No. of paediatric patients	ROSC (%)	Survival to discharge ^a		Favourable neurology ^b % survivor
						% All	% ROSC	
Young and Siedel (1999)	All In-hospital	Systematic Review	All	544	nr	24	nr	60
Moler et al (2009) ^c	ROSC > 20mins	Retrospective	USA	353	(100)	nr	49	77
de Mos (2006)	PICUs only	Retrospective	Canada	91	82	25	31	43
Meaney et al (2006) ^d	PICUs only	Prospective NRCPR	USA	464	50	23	45	64
Nadkarni et al (2006) ^d	All In-hospital	Prospective NRCPR	USA	880	52	27	51	65
Samsom et al (2006) ^d	All In-hospital	Prospective NRCPR	USA	855	50	25	50	88
Tibbals and Kinney (2006)	All In-hospital	Prospective Observational	Australia	111	73	36	49	nr
Lopez-Herce et al (2005)	All In-hospital	Prospective Observational	Spain	213	52	21	41	76
Reis et al (2002)	All In-hospital	Prospective Observational	Brazil	129	64	16	25	90
Parra et al (2000)	Cardiac ICU	Retrospective	USA	32	75	44	58	57
Suominen et al (2000)	All In-hospital	Retrospective	Finland	118	63	18	28	nr
Slonim et al (1997)	PICUs only	Prospective Observational	USA	205	nr	14	nr	nr
Torres et al (1997)	All In-hospital	Retrospective	USA	92	nr	10	nr	78

nr: not reported, ^a hospital discharge or first available outcome (e.g. one month). ^b author defined favourable neurology ^cdata also published in Meert et al (2009). ^dNRCPR different study time periods

1.2.3 Aetiology of cardiac arrest

The underlying cause of cardiac arrest has a profound effect on chances of ROSC and eventual outcome (Young et al, 2004). However, development of a clear definition for categorising causes of cardiac arrest has not yet been achieved (Jacobs et al, 2004). There remains significant variation in the style of coding strategies for allocating cause of arrest and therefore comparisons between studies can be difficult. Large IHCA resuscitation registries tend to code for preceding physiological derangements (e.g. hypotension, metabolic disturbance etc), or associations with post surgical complications (Meaney et al, 2006), whereas OHCA studies tend to allocate by clear diagnostic events (e.g. drowning, poisoning, asphyxia etc). Allocation of OHCA can be made solely on the assessment of immediate first responders and Emergency Medical Service personnel at the scene without additional hospital data (Atkins et al, 2009), or using enhanced data accuracy with national Coroner's data (Deasy et al, 2011a). However, when these two methods are compared they often poorly correlate (Ong et al, 2007; Ong et al, 2006). Finally, variation in the upper age limits of studies can also skew incidence rates for diagnoses more common in adolescents and young adults, for example two OHCA reports by Deasy and colleagues from Melbourne reported incidence of hanging in 0 to 15 years old as 5% (9/193) (Deasy et al, 2010); however, in a similar time period they reported incidence in 0 to 18 year olds of 8% (53/680) (Deasy et al, 2012). Table 1-4 highlights these differences between published studies of OHCA aetiologies.

Additional problems exist with combining aetiologies into groups. Traumatic cardiac arrest has been associated with poorer survival in paediatric patients (Donoghue et al, 2005; Crewdson et al, 2007). However, there exists considerable variation in the allocation of diagnoses to the 'trauma' group. For example, drowning in some is classified as a traumatic aetiology and in others a respiratory aetiology. Therefore, the solution to this problem is not straightforward. Consideration of the population being studied and suitability of categorisation systems for aetiologies will be required to facilitate comparison of the studied population with other relevant published data.

Table 1-4 Published rates of presumed aetiology for OHCA

	Young et al (2004)	Herlitz et al (2007)	Atkins et al (2009)	Moler et al (2009)	Deasy et al (2010)	Deasy et al (2012)	Nitta et al (2011)
No. of patients	n = 601	n= 702	n = 624	n = 138	n = 193	n= 680	n = 875
Age range	0 to <13yrs	0 to <18yrs	0 to <20yrs	1day to <18yrs	0 to <16yrs	0 to <19yrs	0 to <18yr
No obvious cause or unknown	20 (3)	49 (7)	420 (67)	1 (1)	14 (7)	nr	5 (1)
Cardiac	48 (8)	98 (14)	nr	20 (15)	58 (30)	224 (33)	266 (30)
Respiratory	nr	41 (6)	nr	98 (72)	22 (11)	48 (7)	82 (9)
Neurological	35 (6)	nr	nr	5 (4)	nr	27 (4)	27 (3)
Sudden Infant Death Syndrome	136 (23)	207 (29)	38 (6)	nr	40 (21)	129 (19)	nr
Trauma	118 (20)	nr	nr	15 (11)	16 (8)	96 (14)	135 (16)
Drowning	73 (12)	70 (10)	29 (5)	43 (31)	20 (10)	38 (6)	41 (5)
Hanging	nr	nr	34 (6)	0 (0)	9 (5)	53 (8)	22 (3)
Overdose	nr	nr	17 (3)	4 (3)	nr	nr	16 (2)
Foreign body	12 (3)	nr	4 (1)	nr	nr	nr	nr
Suffocation	21 (3)	36 (5)	17 (3)	nr	nr	nr	138 (16)

Values expressed as Number (percent). nr: not reported

1.2.4 Post cardiac arrest syndrome

The recent International Liaison Committee on Resuscitation consensus statement emphasises the existence of the 'post-cardiac arrest syndrome' (Nolan et al, 2008) which was first described by Dr Vladimir Negovsky in 1972 . This syndrome is the consequence of prolonged whole body ischaemia and reperfusion inflammatory injury affecting the brain and myocardium as well as systemic effects similar to those seen in severe sepsis.

The brain is the most vulnerable organ in the body when subjected to hypoxic ischaemia during cardiac arrest. It is the only organ in the human which cannot be replaced or transplanted. Resuscitation during the low-flow phase aims to achieve effective, uninterrupted cardiac compressions and ventilation in order to maintain cerebral perfusion with oxygenated blood. However, even 'excellent' closed chest CPR can only achieve 10 to 25% of normal coronary perfusion and 30 to 40% normal cerebral blood flow (Swenson et al, 1988). The cascade of neurologically damaging processes after cardiac arrest occurs in two phases: 1) Primary neuronal cell death, as a result of immediate (within five to seven minutes) cellular hypoxia and exhaustion of adenosine tri-phosphate (ATP) energy stores and 2) Delayed neuronal cell death which leads to neurodegeneration over hours to days. Damage occurs as a result of a biological cascade leading to: calcium mediated injury in the mitochondria, excitotoxic injury, activation of intracellular enzymes (protease, phospholipase, protein kinase and endonuclease), activation of nitric oxide, formation of oxygen free-radicals, release of free fatty acids, cell death signalling (analogous to developmental apoptosis), gene damage with up-regulation of immediate and late gene expression, and recruitment of inflammatory cells. The consequences of these processes are: impaired cerebrovascular reactivity, cytotoxic cerebral oedema and cerebral hyperaemia (Lopez-Neblina et al, 2005; Eltzschig & Eckle, 2011; Borgens & Liu-Snyder, 2012).

The extent of damage is dependent on numerous factors including the duration of cardiac arrest and the area of the brain which is affected. For example, primary neuronal cell death can affect layers III and IV of the cerebral cortex (watershed areas) causing laminar necrosis or can cause cerebral infarcts via loss of CA1 and CA3 neuronal areas of the hippocampus, basal ganglia and cerebellum (Huang & Castillo, 2008). The subsequent brain injury can

manifest as seizures, cognitive dysfunction, memory loss, myoclonus, signs of stroke, coma, persistent vegetative state and brain death (Nolan et al, 2008). Age dependent selective vulnerability is also present. Apoptosis is greater in the immature brain (less than one year of age) with increased areas of neuronal development with dense regions of excitotoxins (e.g. glutamate) in the hippocampus, which can lead to a relative sparing of the cerebral cortex and cerebellum (Zhu et al, 2005).

Improved basic science knowledge of the post-cardiac arrest syndrome and biological mechanisms for hypoxic ischaemic damage to the brain now enable us to assess potential therapeutic strategies to prevent, inhibit or modulate the harmful effects of brain ischaemia reperfusion and potentially enhance the body's own innate protective mechanisms.

1.3 THERAPEUTIC HYPOTHERMIA

1.3.1 Temperature and cardiac arrest

Humans are homeotherms and have developed a tight temperature homeostatic mechanism, controlled by the hypothalamus to maintain core body temperature between 36.5 and 37.4°C in response to much more extreme external temperature variation (LeBlanc, 1975). Temperature can be reduced through convection, conduction, radiation and evaporation mechanisms, as a consequence of hypothalamus driven changes in arteriolar vasodilatation and sweat gland activation. It can be increased by arteriolar vasoconstriction, piloerection of hair follicles, shivering, muscle use and mitochondrial energy production through brown fat usage. Babies and infants are more vulnerable than adults to heat loss due to larger surface area to weight ratio, lack of shivering mechanism, higher metabolic rates and inability to self-care (i.e. put on more clothes, search out heat source etc). However, they have a developed compensatory mechanism such as heat generation by specialised fat deposits (brown fat).

Disruption to the homeostatic mechanism can be caused by illness, particularly infection, leading to an advantageous hyperthermic (core temperature > 38°C) state, resetting the hypothalamic control level. However, damage to the hypothalamus through brain injury, leading to hyperthermia, has resulted in poor neurological outcome or death after cardiac arrest (Bembea et al, 2010; Suffoletto et al, 2009; Hickey et al, 2000; Zeiner et al, 2001), traumatic brain injury (Natale et al, 2000), hypoxic ischaemic encephalopathy in neonates (Laptook et al, 2008) and stroke (den Hertog et al, 2009; Lakhan & Pamplona, 2012). Hyperthermia has also been independently associated with increased mortality and length of hospital stay in adult neuro-critical care patients (Diringer et al, 2004). International resuscitation guidelines have therefore repeatedly stressed the need to avoid hyperthermia after paediatric cardiac arrest (ILCOR, 2006; Kleinman et al, 2010).

Although the potential benefit of therapeutic hypothermia as a post resuscitation therapy was not fully appreciated until the 20th century, the protective effects of hypothermia in humans had been known for thousands of years. The Egyptians in 2500 BC used low temperatures

to treat injuries and inflammation. Hippocrates (460-370 BC) is reported to have commented that limbs survived longer when covered with ice and snow. Baron Larrey, Napoleon's Surgeon-General, noted that soldiers died more quickly if they were left sitting closer to a fire (Larrey, 1832). However, the use of 'modern' therapeutic hypothermia after cardiac arrest resuscitation was not attempted until the 1950s. This followed successful use of hypothermia under general anaesthesia before cardiac bypass, protecting the brain during cardiac surgery (Bigelow et al, 1950). Initial use after cardiac arrest had varying success. Although, it was believed that temperatures 33 to 30°C and below were required to be beneficial and this led to significant complications (shivering, vasospasm, increased plasma viscosity, bleeding, arrhythmias and lower resistance to infection) (Friedman et al, 1956; Reuler, 1978; Steen et al, 1980; Steen et al, 1979). Therapeutic hypothermia was also used for prolonged periods (up to ten days) in combination with barbiturates, before the development of critical care units, ventilators and monitors, to manage these side effects. Its use continued in the 1960s and 1970s; however, paediatric reports of increased harm, especially during treatment of drowning victims, stopped its use in the 1980s (Bohn et al, 1986; Biggart & Bohn, 1990).

Basic science research 'rediscovered' the benefits of milder therapeutic hypothermia (33 to 34°C) in the late 1980s. Initially by accident, Hossmann et al (1988) identified the beneficial effects of hypothermia (33 to 35°C) prior to a one hour hypoxic insult in cat's electroencephalography recovery. At the same time similar research with dogs discovered the benefits on neurological outcome of hypothermia before cardiac arrest (Safar, 1988). Further studies followed, investigating the use of 'milder' hypothermia (33 to 34°C) *after* prolonged normothermic cardiac arrest, confirming that neurological and histological protection could still be demonstrated and leading to a decade of further experimentation into refining the limits of therapeutic hypothermia (Sterz et al, 1991; Weinrauch et al, 1992; Kuboyama et al, 1993; Safar et al, 1996).

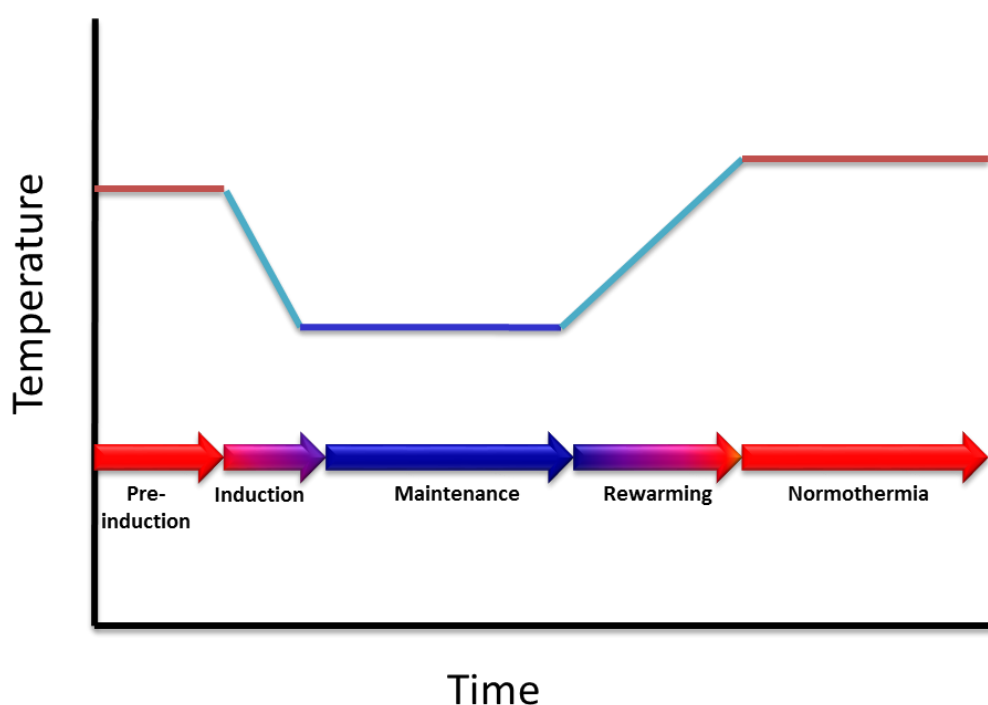
1.3.2 Therapeutic hypothermia - definition

Therapeutic hypothermia is the active reduction of core body temperature to prevent or attenuate the secondary cellular injury after ischaemia reperfusion. Terminology has often

been confusing with descriptors such as 'mild, moderate, severe, extreme, deep etc' referring to variable ranges of temperature (Safar & Behringer, 2003). To clarify this situation the term 'targeted temperature management' has been recommended along with explicit temperature profile (e.g. 32 to 34°C) to improve clarity (Nunnally et al, 2011). In this thesis, patients receiving active targeted temperature management will be referred to as having therapeutic hypothermia, with inclusion of explicit numerical temperature values in parentheses.

Therapeutic hypothermia has three key stages (Figure 1-1): reduction of temperature from current temperature to a lower temperature ("induction"), maintenance of lower temperature for a treatment period ("maintenance") and then return to a normothermic temperature either through active rewarming or through intrinsic physiological control ("rewarming") (Nunnally et al, 2011).

Figure 1-1 Stages of therapeutic hypothermia



1.3.3 How therapeutic hypothermia might work

The pathophysiological mechanism by which therapeutic hypothermia (TH) may exert its neuroprotective effect is complex. There is evidence that it modulates a number of the key biochemical, metabolic and pathophysiological events in the brain which occur after cerebral ischaemia reperfusion injury. These include reduction of cerebral metabolism and balancing out energy failure by the protection of ATP stores during cessation of cerebral blood flow (Steen et al, 1983; Takasu et al, 1996); attenuation of the biosynthesis, release and uptake of excitotoxic compounds such as glutamate and dopamine (Busto et al, 1989; Suehiro et al, 1999); and attenuation of the production of proteins important in apoptosis (Bax and Bcl-2) (Xu et al, 2002; Yenari et al, 2002). TH has also been shown to reduce free radical production (Kil et al, 1996), improve delayed hypoperfusion (Karibe et al, 1994) and be involved in neuronal anti-inflammatory effects (Sutcliffe et al, 2001; Suehiro et al, 2004).

The modulation of these biological cascade mechanisms by therapeutic hypothermia have been demonstrated through experimental animal studies during and after hypoxic ischaemic insults (Busto et al, 1987; Colbourne & Corbett, 1995; Colbourne & Corbett, 1994; Colbourne et al, 1999; Fink et al, 2004; Gunn et al, 1997). However, efficacy is affected by the experimental model (animal species, focal or global ischaemic insult) (van der Worp et al, 2007), duration of ischaemic insult (Chopp et al, 1991), time to commencement of therapeutic hypothermia (earlier to target temperature produces greater effect) (Coimbra & Wieloch, 1994; Busto et al, 1989; Kuboyama et al, 1993; Markarian et al, 1996; Iwata et al, 2007), duration of therapy (longer duration more efficacious especially with increasing delay to start of cooling) (Colbourne et al, 1999), depth of therapy (Iwata et al, 2005), speed of rewarming (too rapid rewarming can reverse neuroprotective effect of therapeutic hypothermia (Suehiro et al, 2003)) and adjunctive anaesthesia or neuroprotective medication (Xenon gas appears to augment neuroprotection of therapeutic hypothermia) (Hobbs et al, 2008; Ma et al, 2005). Also, animal models have limitations when applied to humans. For example, lack of co-morbidities, controlled ischaemic insults and different neuronal development patterns. Therefore, demonstration of efficacy and evaluation of dose

requirement (e.g. depth of hypothermia, duration of therapy, timing of intervention, induction and rewarming rates) in human clinical studies is required.

1.3.4 Clinical studies

Table 1-5 outlines the main therapeutic hypothermia clinical trials in adults, neonates and paediatrics with reported absolute effects sizes. The benefit of therapeutic hypothermia in reducing poor neurological survival after witnessed, ventricular fibrillation cardiac arrest was demonstrated in two landmark RCTs from Europe and Australia in 2002 (HACA, 2002; Bernard et al, 2002). The larger European study recruited 275 patients following out of hospital ventricular fibrillation cardiac arrest. Therapeutic hypothermia was induced within a median of 8 (IQR [4-16]) hours to between 32 to 34°C via surface cooling for 24 hours, followed by rewarming to normothermia. Fifty five percent receiving therapeutic hypothermia had a favourable outcome (survival with good neurological recovery) versus 38% after standard therapy (HACA, 2002). The Australian study recruited 77 patients, again only including patients with ventricular fibrillation induced cardiac arrest (Bernard et al, 2002). Therapeutic hypothermia was induced by paramedics after return of spontaneous circulation using surface ice packs with a median duration to target temperature of 33°C of two hours and continued for 12 hours prior to rewarming to normothermia. Forty nine percent of patients receiving therapeutic hypothermia had survived with a good neurological outcome compared to 26% receiving standard therapy. Numbers needed to treat, to achieve one successful neurological survival, were between four and seven. No serious adverse events were reported after therapeutic hypothermia therapy, although a trend towards increased infection was noted in the European study. However, both studies had weaknesses. The main criticism of the European study was that greater than 25% of the control group experienced a core temperature greater than 38°C, potentially increasing harm in the control group and biasing the study. In the Australian study the quasi-randomisation by alternate day allows bias to be introduced in the randomisation process. No power calculation was performed prior to starting the trial and the study was continued for 12 months after analysis of the first 62 patients as 'outcome was better than previously published' with apparently no statistical adjustment for interim analysis which can therefore lead to inflation of the false

positive rate (Harris et al, 2008). Finally, the significant improvement in good neurological outcome quoted a 'significant' p value of 0.049 using unadjusted odds ratios. However, if the results are reanalysed using the standard χ^2 statistical test, the difference in primary outcome between therapeutic hypothermia and normothermia is non-significant ($p=0.06$).

Despite these weaknesses, two additional small RCTs (Hachimi-Idrissi et al, 2001; Laurent et al, 2005), numerous observational studies and subsequent meta-analyses of all the RCTs (Arrich et al, 2009; Holzer et al, 2005; Cheung et al, 2006) lead to international consensus guidelines recommendations that TH *should be* used in adults after OHCA witnessed, ventricular fibrillation cardiac arrest and *may be considered* in patients presenting after OHCA in a non-shockable rhythm or after IHCA presenting in any rhythm (Peberdy et al, 2010). However, further studies are on-going to investigate the use after IHCA and after non-VF cardiac arrest (NCT00457431; NCT01020916), owing to concerns that the current level of evidence for these groups is incomplete (Nielsen et al, 2011)

Paediatric out-of-hospital cardiac arrest (OHCA) often presents with a non-shockable rhythm. The evidence from the adult population regarding the benefits of TH in this population is more uncertain than if presenting in a shockable rhythm. A systematic review and meta-analysis of two randomised and ten non-randomised studies of the use of TH in adults presenting with a non-shockable initial rhythm, cautiously reported an improved in-hospital mortality rate in pooled patients receiving TH (risk ratio (RR): 0.84 [95% confidence interval (CI); 0.71-0.92]) but no improvement in neurological outcome (RR 0.93 [95% CI; 0.88-1.00]) (Kim et al, 2012). Caution was expressed owing to the high heterogeneity amongst studies, substantial risk of bias and quality of evidence grade as 'very low' using the GRADE profile (Guyatt et al, 2008). The authors concluded that further prospective evaluation of TH after non-shockable cardiac arrest was needed. This recommendation is also supported by the authors of a systematic review performed to update the 2010 ILCOR guidelines (Walters et al, 2011). Therefore, the strength of evidence supporting the use of TH in adult patients groups more closely applicable to the majority of paediatric patients is also weak.

Nielson et al (2011), using critical evidence evaluation and the GRADE profile (Guyatt et al, 2008), also questioned the strength of the evidence regarding the use of TH after adult patients presenting in a shockable rhythm. They re-examined the five randomised controlled trials of TH after shockable rhythms (Bernard et al, 2002; HACA, 2002; Mori et al, 2000; Hachimi-Idrissi et al, 2001; Laurent et al, 2005). They concluded that all trials had substantial risk of bias. Even the largest study (HACA 2002), owing to the exclusion of 92% of screened OHCA patients and lack of control for fever causing potential confounding effect in the control group, could not be graded as low risk of bias. Trial Sequential Analysis of the studies identified that insufficient information had been gained from the combined 424 patients to reject or detect an intervention effect of 16% relative risk reduction of all-cause mortality, therefore recommending further prospective evaluation of TH in patients presenting in both shockable and non-shockable rhythms and ensuring a methodological approach with a low risk of bias.

Over the same time period, neonatologists were investigating the use of therapeutic hypothermia in newborn infants with evidence of hypoxic ischaemic encephalopathy in the first few hours after birth. Six large RCTs have now been performed (Azzopardi et al, 2009; Gluckman et al, 2005; Shankaran et al, 2008; Eicher et al, 2005; Simbruner et al, 2010; Jacobs et al, 2011). Therapeutic hypothermia, targeting 33 to 34°C, was commenced within six hours of birth (and presumed hypoxic insult). This continued for 72 hours in five and 48 hours in the sixth study (Eicher et al 2005) and assessed the composite primary outcome of death or severe disability at eighteen months. Only Shankaran et al (2008) demonstrated a statistically significant improvement in the primary outcome, although one of remaining five studies was terminated early owing to lack of clinical equipoise in clinicians following the publication of earlier studies (Simbruner et al, 2010). Meta-analysis of these studies has, however, shown strong support for therapeutic hypothermia within six hours of birth. There was increased survival with normal neurological function in infants receiving TH in the first 18 months of life than in infants treated by standard care (risk ratio 1.53, 95% CI [1.22 to 1.93]), with a number needed to treat of eight (95% CI 5 to 17) (Edwards et al, 2010). This led to recommendations for adoption of this therapy in national guidelines (NICE, 2010).

Caution regarding the transfer of the positive findings of the adult and neonatal RCTs directly to the paediatric cardiac arrest population is required. The only large, multicentre, RCTs of therapeutic hypothermia in children have been conducted after traumatic brain injury (Hutchison et al, 2008). In the Hypothermia after Paediatric Traumatic Brain Injury Trial, patients receiving therapeutic hypothermia had a worse primary outcome (six month survival with good neurological outcome (PCPC score 1-3) (Fiser, 1992)). Also, a more recent study (CoolKIDS) was terminated early, by the data monitoring committee, due to lack of benefit from therapeutic hypothermia (Personal communication: D. Adelson 2012), although formal results are awaited (NCT00222742). Therapeutic hypothermia has been researched in other conditions at risk of neurological injury in adults. However, systematic reviews of limited RCTs, with significant heterogeneity, also showed no clear benefit after stroke (Lyden et al, 2006; Correia et al, 2000), coronary artery bypass (Rees et al, 2001), or during neurosurgical procedure (Li et al, 2012; Milani et al, 2011).

Table 1-5 Clinical randomised controlled trials of therapeutic hypothermia and effect size

Reference	Study name	Population	Target temperature (°C)	Time to initiate cooling	Cooling duration (hours)	Primary outcome	Primary outcome absolute effect size	Survival only absolute effect size
Bernard et al (2002)		Adult OHCA	32 to 34	a	12	Survival with good neurological outcome	23%	17%
HACA et al (2002)	HACA study	Adult OHCA	32 to 34	b	24	Survival with good neurological outcome	16%	14%
Gluckman et al (2005)	Cool Cap study	Neonatal HIE	34 to 35	≤ 6 hours	72	Death and severe neurological injury	18%	5%
Shankaran et al (2005)	NICHD study	Neonatal HIE	33.5	≤ 6 hours	72	Death and severe neurological injury	18%	13%
Eicher et al (2005)		Neonatal HIE	33.5	≤ 6 hours	48	Death and severe neurological injury	32%	11%
Azzopardi et al (2009)	TOBY study	Neonatal HIE	33 to 34	≤ 6 hours	72	Death and severe neurological injury	8%	1%
Jacobs et al (2011)	ICE study	Neonatal HIE	33 to 34	≤ 6 hours	72	Death and severe neurological injury	15%	13%
Simbruner et al (2010)	neo.nEuro. network	Neonatal HIE	33 to 34	≤ 6 hours	72	Death and severe neurological injury	32%	19%
Hutchison et al (2008)	HypPIT study	Paediatric TBI	32 to 33	≤ 6 hours	24	Death and severe neurological injury	-9%	-9%

a. no inclusion time limit set; cooling commenced in the field by paramedics. b. no inclusion time limit set; cooling commenced in the emergency department after randomisation

1.3.5 Dose of therapeutic hypothermia

The 'pharmacodynamics' of therapeutic hypothermia appear critical to the success and safety of the intervention and intense research (although mostly in animal pre-clinical studies) has focused on the optimal timing, duration, depth and rewarming rates. However, there still remain considerable knowledge gaps regarding the application in clinical practice.

The optimal therapeutic window for TH is not known although beneficial effects in RCTs have been identified when commencement of TH occurs less than six hours after hypoxic ischaemic insult or ROSC (Table 1-5). Evidence from animal studies is that time to target temperature after ROSC should be as short as possible, although benefit has been demonstrated up to six hours after insult (Coimbra & Wieloch, 1994; Busto et al, 1989; Kuboyama et al, 1993; Markarian et al, 1996). Achieving target temperature rapidly after adult cardiac arrest has been associated with improved outcome (Wolff et al, 2009). However, others have observed that in some patients, a faster decline in body temperature to 34°C target appears to predict an unfavourable neurologic outcome, possibly owing to development of a poikilothermic state after more severe brain injury (Haugk et al, 2011).

The depth of temperature used for therapeutic hypothermia is a trade off between the neuroprotective effects of hypothermia and the increasing adverse effects with temperature reduction. As discussed previously, the repeated observations that only a 3 to 5°C reduction in core temperature, reaching 32 to 34°C, was required to produce a sustained neuroprotective effect in animal studies, re-opened the opportunity to successfully use therapeutic hypothermia (Sterz et al, 1991; Weinrauch et al, 1992; Kuboyama et al, 1993; Safar et al, 1996). Table 1-5 demonstrates that the published adult and neonatal therapeutic hypothermia have consistently used this temperature range demonstrating improved neurological outcomes compared to standard therapy. The methods used in these studies, to maintain the target temperature, often resulted in fluctuations of plus or minus 0.5 to 1.0°C around the target temperature. No published post cardiac arrest studies to date have compared two different hypothermia temperatures (e.g. 32 versus 34°C) or a hypothermic temperature with an 'actively' controlled normothermic temperature (e.g. 33 versus 37°C),

rather than allowing usual, standard temperature therapy with the potential to develop hyperthermia (greater than 38°C).

The duration of therapeutic hypothermia required to achieve and sustain neuroprotection after a hypoxic ischaemic injury appears to be exquisitely dependent on the timing after the initial insult. For example, immediate initiation of therapeutic hypothermia resulted in improved neuro-histopathological findings in a rodent ischaemic model with three hours of post-ischaemic hypothermia (30°C) but not when initiation was delayed by 30 minutes (Busto et al, 1989). Rapid initiation of therapy is impractical in the majority of clinical cardiac arrest situations, especially after out of hospital cardiac arrest. Therefore, further exploration of the relationship with duration of therapeutic hypothermia and delay in initiation was explored. Colbourne and colleagues, in a series of experiments using initially a gerbil and then rat model, established that sustained neurological benefit up to one month after ischaemic insult could be maintained if the progressive delay to initiation of therapeutic hypothermia was countered by an increased duration of therapeutic hypothermia. Their final experiments demonstrating that after five minutes ischaemia, 48 hours of therapeutic hypothermia produced neuronal protection, even when initiation was delayed by six hours. However, this benefit was not seen with 24 hours of therapeutic hypothermia (Colbourne et al, 1999; Colbourne et al, 2000). In a fetal sheep model investigating therapeutic hypothermia after hypoxic ischaemic encephalopathy, initiation of therapeutic hypothermia before the on-set of secondary ischaemic seizures (at 5.5 hours) and maintained for 72 hours demonstrated partial neuroprotection; however this was not achieved with a delay of 8.5 hours (Gunn et al, 1998; Gunn et al, 1999).

In adult cardiac arrest RCTs, therapeutic hypothermia has been used for 12 to 24 hours whereas in neonatal RCTs 72 hours duration was chosen. In all scenarios, benefits were seen with therapeutic hypothermia; however, the initial choice of duration for these trials was potentially a 'lucky first guess'. The Australian post cardiac arrest RCT (Bernard et al, 2002), was able to initiate therapeutic hypothermia very quickly after ROSC (median 2 hours) due to starting cooling in the ambulance by paramedics, whereas in the European Hypothermia after Cardiac Arrest study the median delay was 4 hours as cooling was commenced in the

emergency department (HACA, 2002). Therefore, the shorter delay in the Australian study may have theoretically required a shorter duration of therapeutic hypothermia to produce a sustained neurological benefit. Median time to randomisation in two of the neonatal HIE studies was 4 and 4.7 hours with the target temperature reached by 6 hours (Shankaran et al, 2005; Azzopardi et al, 2009). The delay in initiation followed by 72 hours of therapeutic hypothermia successfully increased survival with good neurological outcome at 18 months; however, comparisons between different durations of therapeutic hypothermia have not been performed after either HIE or cardiac arrest. Current ILCOR therapeutic hypothermia recommendations are for 12 to 24 hours of therapy after cardiac arrest and for 72 hours after neonatal HIE.

Controlled rewarming and avoidance of overshoot hyperthermia ($>38^{\circ}\text{C}$) are required to prevent haemodynamic instability, rapid electrolyte changes and worsening of neurological injury. Rapid rewarming can result in peripheral vasodilatation and hypotension. The increased metabolic oxygen demand during rapid rewarming and the required increase in cardiac output may not be met by a potentially damaged myocardium after the initial cardiac arrest.

1.3.6 Available methods of temperature control

The current methods of cooling can be divided into surface and internal methods (Table 1-6). They each aim to reduce, maintain or increase brain temperature through a combination of: conduction, convection, radiation and evaporation.

Simple methods include applying ice packs or wet linen to the skin to areas of high vascular blood supply: groins, neck, torso and head. This cools the superficial blood which flows and subsequently cools deeper, core structures. These methods are labour intensive requiring frequent changing of linen and icepacks as they become warmer and less efficient, although they are cheap and effective in resource limited environments. Advances to these methods include air and water blankets (Hoedemaekers et al, 2007). These cover the patient's skin, and a liquid (or air) is cooled mechanically and flows through the blanket. This achieves a more consistent temperature in the blanket and the temperature can be automatically

increased or decreased in response to feedback from the patient's core measured temperature, thereby achieving greater stability. A limitation to this method is that patients become vasoconstricted due to contact with the cold blankets and therefore redirect capillary blood to deeper tissues, reducing the efficiency of cooling.

Another surface cooling method is selective head cooling via a tight fitting cap with cold liquid circulating through. This only cools the head avoiding systemic cooling side effects. The external cooling is transmitted to deeper structures, although the efficacy of this method is not clear. This method has been used in neonatal studies of HIE and adult cardiac arrest studies, but has not been used in the paediatric cardiac arrest population (Hachimi-Idrissi et al, 2001; Gunn et al, 2005). Transnasal evaporative cooling has also been shown to effectively reduce core and tympanic temperature during and after adult cardiac arrest (Castren et al, 2010).

Invasive cooling involves additional devices directly accessing blood vessels and the circulation. A simple, safe and effective method is the use of intravenous normal saline fluid, cooled to 4°C ('ice-cold') and injected as a bolus. This method has been demonstrated to be safe and effective in the pre-hospital setting in adult cardiac arrest patients (Kim et al, 2005; Bernard & Rosalio, 2008) and in the paediatric critical care environment (Fink et al, 2012; Kelly et al, 2010). This method is effective at temperature reduction but may not be adequate for maintenance; requiring additional methods to continue temperature control (Kliegel et al, 2007; Larsson et al, 2010).

Intravenous cooling catheters have a jacket of circulating cold fluid which flows in direct proximity of venous blood, continuously cooling or warming the patient. Intravascular cooling catheters are useful and effective in the adult population; however, are not manufactured in sizes suitable for the smaller veins in most children and there are concerns with the increased risk of venous thrombosis (Hinz et al, 2007; Lau et al, 2010).

Diverting blood flow out of the patient's circulation via large catheters and using external temperature controlling devices is also very effective although very invasive. This method is possible during extracorporeal support (e.g. cardio-pulmonary bypass or extracorporeal life

support (ECLS)). Both of these methods involve high volumes of blood (100-150mls/kg/min) being removed, oxygenated and returned to the patient after having flowed through a temperature controlling water-bath. These methods are used when patients require rewarming after extreme hypothermic arrest (temperature less than 30°C) (Walpoth et al, 1990; Saxena et al, 2009) or during extracorporeal life support CPR (ECPR), a method of restoring cerebral perfusion during refractory cardiac arrest resistant to advanced life support resuscitation (Huang et al, 2008; Le Guen et al, 2011a; Raymond et al, 2010).

Table 1-6 Summary of temperature controlling devices

Group	Method of temperature control
Surface	Ice packs to skin Wet linen Water blanket Air blanket Whole body water submersion Nasopharyngeal cooling Selective head cooling
Internal	Intravascular cooling device Intravenous ice-cold (4°C) saline Extracorporeal life support circuit Cardio-pulmonary bypass Haemofiltration circuit Intrathecal infusion (animal study only) Carotid artery infusion (animal study only)

1.4 FEASIBILITY CHALLENGES OF PAEDIATRIC CRITICAL CARE RANDOMISED CONTROLLED TRIALS

Clinical research involving children has always been a challenge to clinicians, parents and the children themselves. There can be a considerable conflict between society's protection of children from health care research and the quest to advance and improve our understanding of paediatric practice (Halpern et al, 2009). Valid concerns regarding the legal and ethical restrictions involved in paediatric research and the burdensome bureaucracy have limited progress, as have methodological constrictions, most importantly, the number of subjects (Macrae, 2009). However, reliance upon extrapolated 'adult' evidence to paediatric practice, where physiological, developmental and disease aetiology differences are present, is now acknowledged as being unacceptable (Knellwolf et al, 2011).

1.4.1 Randomised controlled trials

Randomised controlled trials (RCTs) remain the gold standard methodological approach to comparing the clinical and cost effectiveness of two interventions and determining a cause-effect relationship between treatment and outcome. Important benefits of RCTs over observational studies include: random allocation to intervention groups which ensures no systematic difference in known and unknown factors between groups, all intervention groups receive identical treatment except for the experimental treatment and patients are analysed within the group they were originally allocated (Sibbald & Roland, 1998). However, critical care RCTs in adults, have repeatedly failed to deliver evidence of beneficial treatments. Ospina-Tascon et al (2008) in a systematic review of critical care trials using mortality as an outcome, identified only 10 out of 72 studies showing benefit, with 55 demonstrating no effect. Many factors have been identified including: use of heterogeneous populations, lack of biological plausibility, use of unblinded RCTs, over estimating potential treatment effects based on observational study evidence and importantly under-powering of studies through failing to recruit to target (McAuley et al, 2010). This has led some observers to even recommend abandoning RCTs in critical care altogether (Vincent, 2010). Because paediatric critical care has many fewer patients than adult critical care, this problem is potentially even

greater. However, recent successful international and UK multicentre collaborations, in paediatric critical care RCTs, set a good basis for future collaborative endeavours (Macrae et al, 2010; Hutchison et al, 2008; Lacroix et al, 2007). Establishment of UK paediatric critical care networks (e.g. PICANet (Paediatric Intensive Care Audit Network) and PICS-SG (UK, Paediatric Intensive Care Study Group)) should also enhance trial success and justify choosing the RCT as the ideal method for investigating the presence of a beneficial effect with therapeutic hypothermia.

1.4.2 Risk-stratification and minimisation in randomised controlled trials

Simple randomisation should theoretically ensure treatment groups in a RCT are comparable. However, in small to medium sized RCTs (e.g. less than 400 patients) there is a risk of misbalanced groups in terms of numbers in each group and similarity between base-line characteristics (Kernan et al, 1999). In addition, as previously discussed, individual cardiac arrest patients can have important differences potentially affecting both their chance of good outcome and response to an intervention. Simple randomisation followed by the conventional method of sub-group analysis, to explore differences in treatment effect, based on individual patient characteristics one at a time (e.g. male versus female) has been found to perform badly in heterogeneous populations and has limited statistical power (Brookes et al, 2001).

The approaches to dealing with these problems include 1) permuted block randomisation, 2) risk-stratified randomisation, 3) minimisation, 4) standard post result subgroup analysis and 5) risk-stratified post result analysis.

Permuted block randomisation is a simple method and strongly recommended to ensure balanced allocation of numbers of patients in each intervention group but does not address any individual patient characteristic. Risk-stratified randomisation uses pre-defined important prognostic variables, identified at randomisation, and grouped into strata according to the variable. The patients in each stratum are then randomly allocated to interventions, thereby preventing imbalance for prognostic features in the two treatment groups. The advantages to this method include assurance that comparison groups are similar with respect to known

prognostic variables, prevention against type I and type II errors and increased efficiency of a trial ensuring the sample population will be effectively balanced or allowing a reduction in the sample size requirement (Kalish & Begg, 1985; Hernandez et al, 2004). Risk stratification is essential in studies with fewer than 100 patients, desirable if fewer than 400, although less important for much larger trials. Chosen prognostic variables should be identified before the trial starts (Bulpitt, 1988) and in general, fewer variables are better (e.g. three or four) as more patients will be allocated to each stratum, improving statistical efficiency (Byar et al, 1976). The use of a multivariate prediction tool for stratification as opposed to individual variables may be more advantageous (Miettinen, 1976). The combination of multiple prediction variables may be more reliable, it may create greater distinction amongst risk groups as variables may be summative or synergistic on outcome and the number of strata could be reduced. However, an important disadvantage to consider with regards emergency, cardiac arrest trials is the increased administrative burden in collecting data for the variables in the prediction tool and therefore potentially complicating or delaying emergency treatment (Kernan et al, 1999).

Minimisation is another method to avoid imbalance between numbers of patients in each treatment group over a number of factors (Taves, 2010). It uses information about patients already in the trial to influence treatment for new patients. It can be particularly useful in small trials (less than 100 patients) and greater than three prognostic factors (Pocock & Simon, 1975). It requires pre-specified covariates entered into an algorithm to allocate intervention. Its use is supported in the Consolidated Standards of Reporting Trials (CONSORT) (Schulz et al, 2010). Minimisation is the only accepted replacement of randomisation; however, an additional randomisation process is recommended when the intervention cannot be blinded to avoid selection bias (e.g. therapeutic hypothermia) (Taves, 2010).

Subgroup analysis assesses differences in treatment effect between different subpopulations of patients. However, reliance on sub-group analysis, to identify if the findings from a RCT sample population are generally applicable to a wider population, has also been shown to be, at times, wrong (Feinstein & Horwitz, 1997). Especially if multiple

characteristics interact and affect the likelihood of a treatment being beneficial or harmful (Hayward et al, 2006). Therefore, some statisticians advocate the use of multivariable, risk-stratified analysis as a supplement or alternative method to conventional subgroup analysis (Hayward et al, 2006; Rothwell, 1995; Kravitz et al, 2004). Risk-stratified analysis requires several patient attributes to be combined into a score that describes a single dimension of risk along which a treatment effect is likely to vary (Kent & Hayward, 2007). The score should ideally be an externally created, validated model. A previous example of the use of risk-stratified analysis was by Kent et al (2002) who identified a subgroup of patients who did not benefit from tissue plasminogen activator (tPA) in the Global Utilisation of Streptokinase and tPA for occluded coronary arteries (GUSTO) trial. The original trial demonstrated a decrease in mortality if treated with tPA (GUSTO., 1993). The original subgroup analysis did not identify subgroups that did not benefit. However, with a new validated model, this was possible through risk-stratified analysis and allowed more individualisation of patients, identifying who may benefit from treatment and where benefit may be outweighed by net harm (Kent et al, 2002).

In summary, risk stratified randomisation and minimisation are both important techniques to avoid imbalance in RCT treatment groups, improve efficiency of a trial and minimise type I and II errors. Additionally, risk-stratified analysis may also improve identification of whether a RCT is applicable to individual patients. Identification of important prognostic variables for paediatric cardiac arrest patients prior to a RCT, will allow development of these essential tools.

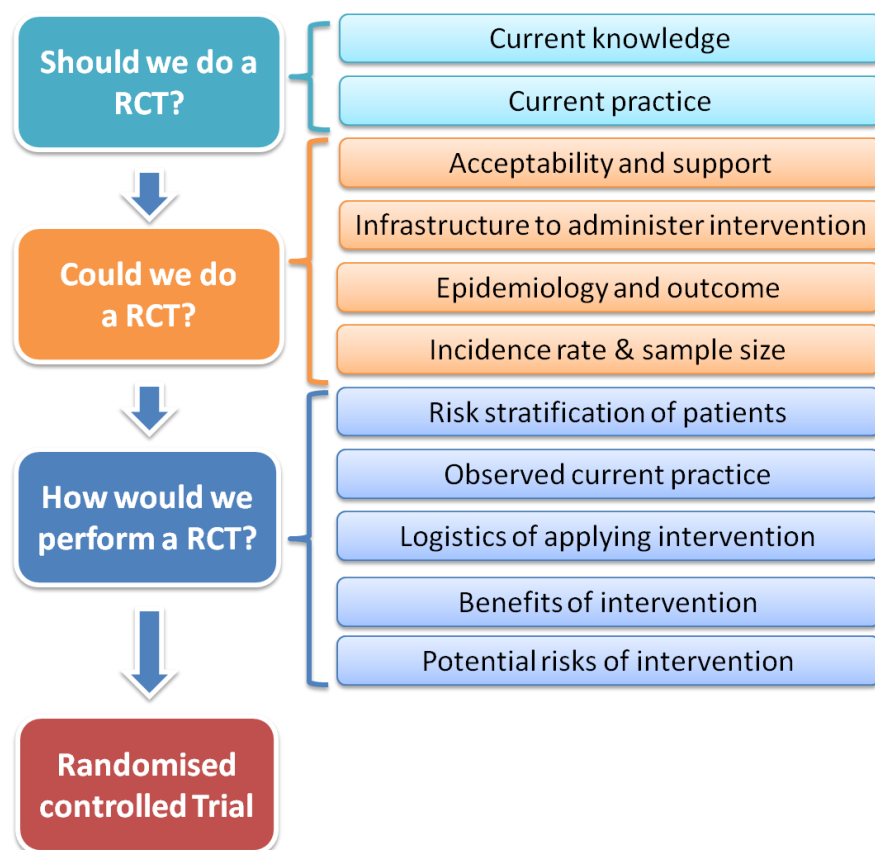
1.4.3 Stepwise approach to randomised controlled trial development

A stepwise approach to RCT development has been recommended to successfully assess the feasibility of performing a RCT and to minimise the risks of failure (Figure 1-2) (Marshall & Cook, 2009). This begins with articulation of a study question and research objective. The next step is to decide if the research objective *should* be followed. This requires an assessment of what is currently known through a systematic review or meta-analysis of the literature in conjunction with an evaluation of current clinical practice. The importance of the research question to the health care community requires investigation with clarification of

two important areas. First, is the original research question important and worthwhile in the context of a resource limited health service and secondly, does clinical equipoise exist amongst clinicians? Clinical equipoise has been defined as 'there existing an honest, professional disagreement among expert clinicians about the preferred treatment' (Freedman, 1987). Without clinical equipoise, randomisation of patients into a RCT to compare two treatments (where the body of belief is that one therapy is more efficacious than the other), is unethical (Freedman, 1987). Often individual clinicians have strongly held opinions; however, a state of community equipoise may exist. Therefore, it is fundamentally important to demonstrate variability in practice to establish clinical equipoise (Marshall & Cook, 2009).

Observational studies follow to allow assessment of prevalence or incidence rate of a disorder and risk factors associated with the condition and treatment proposed. This is the step where the question is asked, '*could* the RCT be performed?' During this stage, areas where previous RCTs have been shown to fail can be investigated. For example, are there sufficient patients to recruit to a study and therefore be adequately powered to demonstrate an effect? Are the right patients identified or is it a question of severity of the condition requiring risk-stratification? Is the timing of the intervention important and is it feasible to implement the therapy within those time constraints? Are interventions effective in observational studies? Finally, are the risks and adverse effects of an intervention acceptable? (McAuley et al, 2010; Vincent, 2010). During the observational studies, opportunities will also arise to enhance the basic understanding of the condition and the intervention evaluated, beginning the stage of assessing *how would* a RCT be performed. This can then input into the design and development of a study protocol of a RCT. With acknowledgement that RCTs are not the final step and translation of knowledge into clinical practice poses an even greater hurdle (Kahn, 2009).

Figure 1-2 Stepwise model of RCT feasibility assessment (adapted from a programmatic research model) (Marshall et al 2009)



2 Study Aims and Outline of the Thesis

"First comes thought; then organisation of that thought, into ideas and plans; then transformation of those plans into reality.

The beginning, as you will observe, is in your imagination"

Napoleon Hill (American Author Born 1883)

2.1 STUDY AIMS

Survival with a good neurological outcome after paediatric cardiac arrest remains rare despite advances in resuscitation practices in the UK. Neuro-protective therapies are desperately needed to improve these poor outcomes. Therapeutic hypothermia is a potential therapy; however, paediatric evidence appears limited. Demonstration of increased efficacy and cost effectiveness in children of therapeutic hypothermia compared to standard 'normothermic' temperature therapy requires a randomised controlled trial (RCT). Before this can be undertaken in the UK, the following feasibility questions need to be addressed: should we, could we and how would we design a RCT?

The main research questions of this thesis are therefore:

1. Is there currently sufficient evidence to support or refute the beneficial effects of therapeutic hypothermia after paediatric cardiac arrest?
2. What is currently practiced in the UK regarding therapeutic hypothermia after paediatric cardiac arrest?
3. Does clinical equipoise exist amongst the paediatric intensive and emergency care communities?
4. What is the current epidemiology of children who are successfully resuscitated and admitted to PICU after cardiac arrest in the UK?
5. What is the potential size of the paediatric post-cardiac arrest population admitted to PICU and is this sufficient for a UK RCT of therapeutic hypothermia?
6. Can outcome after paediatric cardiac arrest be predicted to assist risk-stratification of patients in a RCT?
7. Can therapeutic hypothermia be implemented quickly, safely and consistently in children?
8. Does therapeutic hypothermia improve survival after out of hospital cardiac arrest and are there significant physiological adverse effects?

2.2 OUTLINE OF THE THESIS

This thesis presents a consecutive series of studies answering the above questions regarding the feasibility of performing a RCT of therapeutic hypothermia after paediatric cardiac arrest in the UK and is outlined in Figure 2-1.

Chapter 3 starts with a systematic literature review conducted in accordance with strict Cochrane methodology to investigate the current and on-going research supporting the use of therapeutic hypothermia after paediatric cardiac arrest, in order to justify the need for further research.

The current use of therapeutic hypothermia by UK paediatric critical care and emergency medicine specialists is investigated in Chapter 4, allowing an opportunity to explore current practice and the important position of clinical equipoise amongst clinical staff.

Chapter 5 allows a broader look at the paediatric cardiac arrest population in the UK. Through the use of national PICU admission data of IHCA and OHCA patients, an epidemiological analysis of the UK cardiac arrest population is possible. Differences between IHCA and OHCA patients can be assessed and essential population numbers can be collected to calculate whether the UK has a large enough paediatric cardiac arrest population to adequately recruit to a RCT.

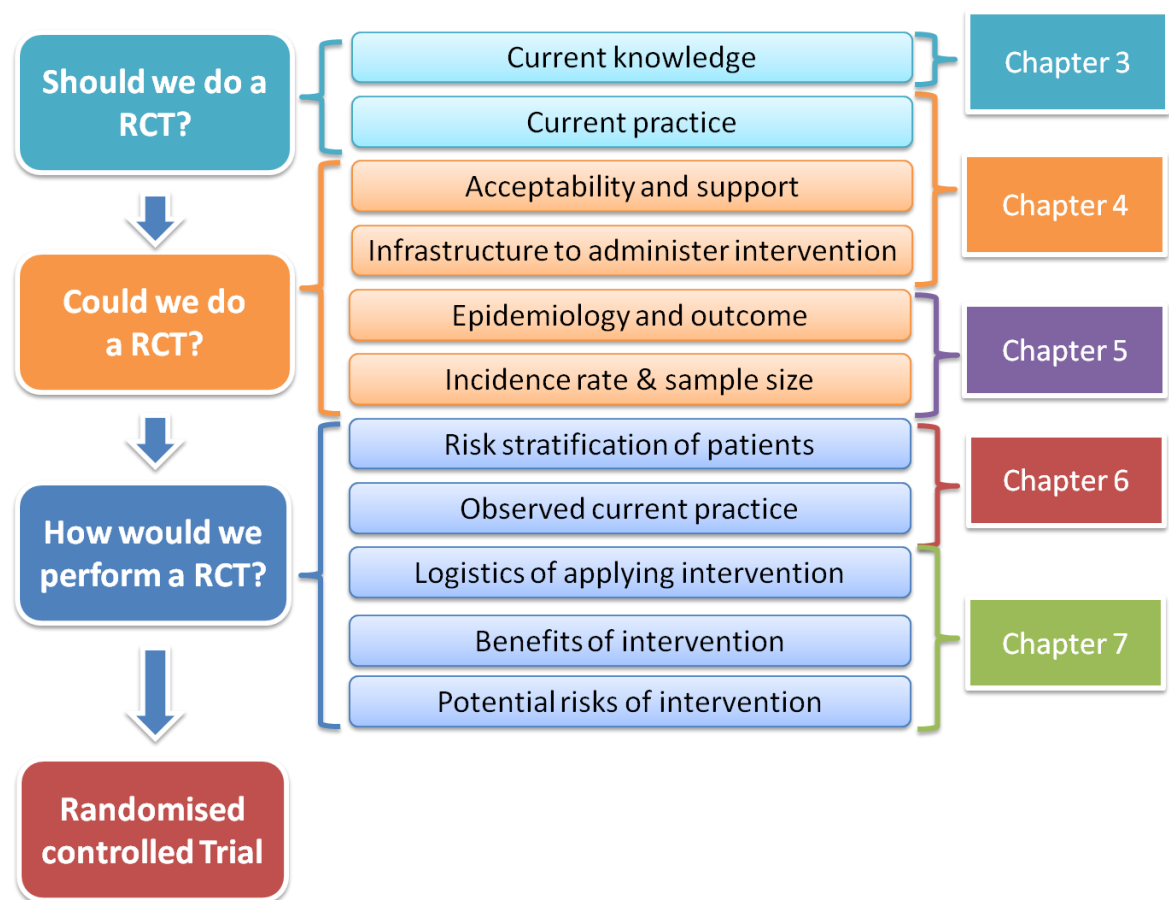
A more in-depth analysis of patients admitted to three large PICUs after OHCA will follow in Chapter 6. Factors available at the time of resuscitation and at admission to PICU will be analysed in an attempt to identify important prognostic factors for survival. This would then allow selection or risk-stratification of post-OHCA patients randomised in a future study.

In Chapter 7, through the use of a subset of OHCA patients from Chapter 6, post cardiac arrest therapeutic hypothermia can be compared to standard temperature therapy. This will

allow an assessment of efficacy and safety of therapeutic hypothermia in addition to identifying practical barriers to implementing the therapy in a future research setting.

Finally, based on the previous exploratory parts of this thesis, a summary of findings and a conclusive answer to the feasibility research question will be presented. Short comings of the thesis will be discussed and a proposal for future research.

Figure 2-1 Stepwise model of RCT feasibility assessment mapped to thesis chapters



3 Hypothermia for neuroprotection in children after cardiac arrest: a systematic Cochrane review.

“Absence of evidence is not evidence of absence”

Leonardo da Vinci (painter, scientist & mathematician: Born 1452)

Part of this chapter has been published in:

Scholefield B, Morris K, Duncan H, Davies P, Gao-Smith F, Khan K. Hypothermia for neuroprotection in children after cardiopulmonary arrest (protocol). *Cochrane Database of Systematic Reviews* 2011, Issue 11. Art. No.: CD009442. DOI: 10.1002/14651858.CD009442. (Appendix 9.4 p305)

3.1 ABSTRACT

3.1.1 Introduction

Cardiac arrest in paediatric patients often results in death or survival with severe brain injury. Therapeutic hypothermia, lowering of core body temperature to 32 to 34 °C, may reduce injury to the brain in the period after the circulation has been restored. This therapy has been effective in neonates with hypoxic ischaemic encephalopathy and adults after ventricular fibrillation cardiac arrest. The effect of therapeutic hypothermia after cardiac arrest in paediatric patients is unknown.

3.1.2 Aims

To assess the clinical effectiveness of therapeutic hypothermia after paediatric cardiac arrest.

3.1.3 Methodology

We searched the Cochrane Anaesthesia Review Group Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, 2011 issue 11); Ovid MEDLINE (1966 to December 2011); Ovid EMBASE (1980 to December 2011); Ovid CINAHL (1982 to December 2011); Ovid BIOSIS (1923 to December 2011); Web of Science (1945 to December 2011). We searched the trials registry databases for ongoing trials. We also contacted international experts in therapeutic hypothermia and paediatric critical care to locate further published and unpublished studies.

We planned to include randomised and quasi-randomised controlled trials comparing therapeutic hypothermia with normothermia or standard care in children, aged 24 hours to 18 years, after paediatric cardiac arrest. Two authors independently assessed articles for inclusion.

3.1.4 Results

We found no studies that satisfied the inclusion criteria. We found four on-going randomised controlled trials which may be available for analysis in the future. We excluded 18 non-

randomised studies. Of these 18 non-randomised studies, three compared therapeutic hypothermia with standard therapy demonstrating no difference in mortality or proportion with good neurological outcome and a narrative report is presented.

3.1.5 Conclusion

Based on this review, we are unable to make any recommendations for clinical practice. Randomised controlled trials are needed and the results of on-going trials will be assessed when available.

3.2 INTRODUCTION

Therapeutic hypothermia has been shown clinically to be neuroprotective in neonates with hypoxic ischaemic encephalopathy secondary to birth asphyxia (Jacobs et al, 2007) and in adults (greater than 18 years old) after witnessed, ventricular fibrillation cardiac arrest (Holzer et al, 2005; Arrich et al, 2009). Its role after cardiac arrest in children has not been established although the International Liaison Committee for Resuscitation guidelines recommend consideration of its use in this setting (Kleinman et al, 2010). This systematic review of the literature will investigate the neuroprotective effects of therapeutic hypothermia in children after cardiac arrest.

3.2.1 Description of the condition

Cardiac arrest in children is a devastating event. Survival rates to discharge from hospital for children who suffer an IHCA are 15% to 30% whilst those who suffer an OHCA have a worse survival rate (5% to 12%) (Donoghue et al, 2005; Nadkarni et al, 2006). Only 0.3% to 4% of children who suffer an OHCA survive neurologically intact (Donoghue et al, 2005).

Neurological consequences of hypoxic ischaemic damage to the brain range from mild concentration, attention and short-term memory problems to much more severe damage to the cerebral cortex, hippocampus, basal ganglia and cerebellum. Severe damage can result in significant long-term loss of function with development of cerebral palsy, blindness, seizures, hypothalamic and pituitary insufficiency. Very severe damage can produce a persistent vegetative state or be fatal. Those children who do survive often have significant neurological disability with resultant emotional, time and financial impacts on themselves, their families, their educational and care needs, rehabilitation and society as a whole (Duncan & Frew, 2009; Ronco et al, 1995; Morris et al, 1993);

Neurological outcomes are often assessed by the use of the Paediatric Cerebral Performance Category (PCPC) score (Fiser, 1992) (Table 3-1). The PCPC scores can classically be combined into a good outcome (PCPC 1 and 2) and poor outcome (PCPC 3 to 5). If children with preceding disability are included then a good outcome may be recorded

as no change from baseline. Other neurological outcome scores, for example the Vineland Adaptive Behaviour Scales (Sparrow S et al, 1984), have also been validated for use in assessing the neurological outcomes in children.

Table 3-1 Paediatric Cerebral Performance Category (Fiser, 1992)

	Category (neurological function)	Description
1	Normal	Healthy alert, regular classroom
2	Mild disability	Age appropriate interactions, but possible mild neurologic deficit, grade not appropriate
3	Moderate disability	Independent activity of daily living but special educational classroom or learning deficit
4	Severe disability	Conscious but dependent on others because of neurologic deficit
5	Coma/ Persistent vegetative state	Any degree of coma; unconscious, unaware
6	Dead	

The aetiology for paediatric cardiac arrest is different to that of adults, with respiratory disorders leading to hypoxia often preceding cardiac arrest in children (Young et al, 2004). The commonest causes of OHCA in children are sudden infant death syndrome, drowning and trauma (Atkins et al, 2009). IHCA are predominantly secondary to respiratory insufficiency, hypotension, hypoperfusion, congestive cardiac failure or infection (Nadkarni et al, 2006). The neonates studied while receiving therapeutic hypothermia after hypoxic ischaemic encephalopathy often did not have a cardiac arrest and therefore retained some cerebral blood flow in comparison to the absent cerebral blood flow during cardiac arrest (Azzopardi et al, 2009). Therefore, the pattern of neurological injury in adults and neonates may be different to children and the efficacy of therapeutic hypothermia may be altered.

3.2.2 Description of the intervention

Therapeutic hypothermia is defined as the process of lowering core body temperature to between 32 and 34 degrees Celsius. Therapeutic hypothermia can be administered through systemic cooling (by surface or invasive methods) and selective surface head cooling. Sedation and often neuromuscular blockade are required to tolerate the intervention and avoid shivering.

3.2.3 Why it is important to do this review

Cardiac arrest in children is an important condition with a poor survival rate and a high chance of neurological injury leading to significant long-term impact on individuals, families and society. There are currently no interventions available to decrease neurological injury other than supportive care in the intensive care unit, which is why this evaluation is important. Paediatric specific data are needed regarding the effect of therapeutic hypothermia owing to the different aetiology and resultant pathophysiology compared to adults and neonates. Therapeutic hypothermia is used by some in paediatric critical care after cardiac arrest (Haque et al, 2006; Scholefield et al, 2010) and a meta-analysis of the clinical trial data is therefore highly important.

3.3 AIMS

1. To systematically review the literature and, if feasible, perform a meta-analysis concerning the neuroprotective effects of therapeutic hypothermia after cardiac arrest in children.
2. To determine whether therapeutic hypothermia is effective in improving the primary outcome of good neurological survival after cardiac arrest in children and the secondary outcome of improving overall survival.
3. To determine the extent of adverse effects and effects on quality of life in this context.

3.4 METHODOLOGY

3.4.1 Criteria for considering studies for this review

3.4.1.1 *Types of studies*

We planned to include randomised controlled trials (RCTs) and quasi-randomised controlled trials evaluating therapeutic hypothermia as a neuroprotective intervention after cardiac arrest in children. We excluded non-randomised studies from the meta-analysis but provided a narrative summary of these studies in the review's discussion section.

3.4.1.2 *Types of participants*

We planned to include all studies with children who are successfully resuscitated after a cardiac arrest in any setting. We sought to include neonates older than 24 hours of age and with a corrected gestational age of greater than or equal to 35 weeks, children and adolescents up to their 18th birthday. We excluded neonates whose cardiac arrest occurs at the time of birth and adults greater than 18 years of age as these have been studied separately (Arrich et al, 2009; Jacobs et al, 2007) and the presumed cause of the cardiac arrest is different to children.

3.4.1.3 *Types of interventions*

Therapeutic hypothermia, regardless of how body temperature is reduced, applied within a few hours after return of spontaneous circulation after cardiac arrest. Therapeutic hypothermia is defined as a target temperature of 32 to 34 degrees Celsius. We defined the control intervention as treatment according to the standard treatment after cardiac arrest at the time of the trial.

3.4.1.4 *Types of outcome measures*

3.4.1.5 *Primary outcomes*

1. Best neurological outcome at hospital discharge and within the first year as assessed by the Paediatric Cerebral Performance Category score and other validated outcome scores for use in children (e.g. Vineland Adaptive Behaviour Scales)

3.4.1.6 *Secondary outcomes*

1. Survival to intensive care discharge
2. Survival to hospital discharge
3. Survival up to six months and long-term survival (long term defined as greater than one year)
4. Adverse event incidents as reported by authors
5. Quality of life indicators at six months and at long term

3.4.2 *Search methods for identification of studies*

3.4.2.1 *Electronic searches*

We searched the Cochrane Anaesthesia Review Group Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, latest issue); Ovid MEDLINE (1966 to December 2011); Ovid EMBASE (1980 to December 2011); Ovid CINAHL (1982 to December 2011); Ovid BIOSIS (1923 to December 2011); Web of Science (1945 to December 2011).

The Ovid MEDLINE specific search terms are described in Appendix 9.1 (p299). We based the search strategies for the other databases on the one for MEDLINE. We combined the Ovid MEDLINE and EMBASE searches with the sensitive strategies described in Section 6.4 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins JPT et al, 2011) to search for RCTs.

BIOSIS and Web of Science contain book articles and abstracts of conference presentations published in a wide range of relevant specialist journals.

We did not use language or publication type restrictions.

3.4.2.2 *Searching other resources*

We searched the bibliographies of all retrieved and relevant publications identified by these strategies for further studies. We searched the Current Controlled trials (<http://www.controlled-trials.com/>), Clinical Trials (<http://clinicaltrials.gov/>), Trials Central (<http://www.trialscentral.org>), Chinese clinical trials registry (<http://www.chictr.org/en/proj/search.aspx>), International World Health Organisation (WHO) trials registry (<http://apps.who.int/trialsearch/>) databases of ongoing trials. We searched Zetoc (<http://zetoc.mimas.ac.uk/>) and OpenSIGLE (<http://opensigle.inist.fr/>), and contacted experts in the field to search for any other published or unpublished literature and on-going research.

3.4.3 *Data collection and analysis*

3.4.3.1 *Selection of studies*

Potentially eligible published studies were located based on screening of title and abstract by two authors (Barnaby Scholefield (BS) and Heather Duncan (HD)). Potentially eligible on-going trials were located on screening title and trial description by two authors (BS and Kevin Morris (KM)). We obtained full copies of potentially eligible studies. There was no blinding to the journal, the authors or the institution. Three authors (BS, KM and HD), acting independently, decided on inclusion or exclusion of studies based on predefined inclusion and exclusion forms. We resolved disagreements by discussion.

3.4.3.2 *Data extraction and management*

We intended to extract data from eligible studies and summarized them in a data extraction sheet (Appendix 9.2, p301). We also intended to include baseline data on demographics of study and control group participants. This included age and gender. In addition, we planned to extract the following information regarding the actual cardiac arrest; location, aetiology, duration of arrest; and time to return of spontaneous circulation for each group. We planned to record data on the intervention; time to implement intervention; duration, and type of

temperature control method. The temperature of the study group and control group at the start of a study, during intervention and after the intervention were recorded. We also planned to record the healthcare setting in which the interventions were performed. In addition, duration of follow up and numbers lost to follow up were planned to be extracted as well as outcomes.

All data regarding the interventions studied were independently extracted by two authors (BS and KM or HD). We resolved disagreements by discussion. We intended to contact primary authors to obtain missing data or to gain clarification.

3.4.3.3 *Assessment of risk of bias in included studies*

After we included all available eligible studies in the review, we proposed to assign two authors (BS and KM or HD) to independently assess each study using The Cochrane Collaboration's tool for assessing risk of bias (Higgins JPT et al, 2011). We planned to assess six domains: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other bias (Appendix 9.2, p301). Completing a risk of bias table for each eligible study. Any disagreement was planned to be discussed amongst authors and consensus agreed. We intended to present our assessment of risk of bias using a 'risk of bias summary figure', which presents all of the judgments in a cross-tabulation of study by entry.

3.4.3.4 *Measures of treatment effect*

For dichotomous outcomes, we planned to express the estimate of effect of an intervention as the risk ratio (RR) together with the 95% confidence interval (CI). For continuous outcomes, we planned to use mean differences (MD) and standard deviations and summarize the data for each group using mean differences and 95% CIs.

3.4.3.5 *Unit of analysis issues*

We did not anticipate unit of analysis issues.

3.4.3.6 *Dealing with missing data*

If data were missing from trial reports we attempted to contact the original investigator for additional data. Where there were missing data, we planned to 'impute' and carried out a sensitivity analysis between studies in which data were 'imputed' for an intention-to-treat (ITT) analysis assuming that all missing participants experienced the event, or that all missing participants did not experience the event.

3.4.3.7 *Assessment of heterogeneity*

We judged clinical heterogeneity, in particular in the application of therapeutic hypothermia. If significant clinical heterogeneity existed, pooling of data was not done; the data from individual studies is presented in a tabular format. We planned to test for statistical heterogeneity using visible inspection of the forest plot and the I^2 statistic (Higgins JPT et al, 2011). We considered an I^2 statistic > 50% as significant statistical heterogeneity and a value < 25% was considered ignorable statistical heterogeneity.

3.4.3.8 *Assessment of reporting biases*

We planned to assess risk of reporting bias by producing a funnel plot if there were sufficient number of included studies (more than 10). We took the following steps to reduce reporting bias.

1. Searching of multiple databases, trial registries and conference proceedings as described above.
2. Applying no language restriction.
3. Excluding duplicate reports of the same study to avoid duplication bias.

3.4.3.9 *Data synthesis*

We intended to summarize the aims, methods and outcome measures of interest (neurological outcome, mortality, adverse events and quality of life indicators) for each included study. We expressed the outcome measures of interest for survivors relative to non-survivors as the risk ratio (RR).

For both dichotomous and continuous data we planned to undertake a meta-analysis using a random-effects method with inverse variance. We planned to perform a sensitivity analysis by comparing this with a meta-analysis using a fixed-effect method with inverse variance.

We planned to use data at the aggregate (study) level.

3.4.3.10 Subgroup analysis and investigation of heterogeneity

We proposed to perform subgroup analysis on the following variables if the data could be extracted from included studies.

1. Age and sex.
2. Method of inducing therapeutic hypothermia (systemic cooling versus selective head cooling).
3. Location of arrest (in-hospital versus out-of-hospital arrest).
4. Duration of intervention.
5. Delay to induction of therapeutic hypothermia (less than six hours versus greater than six hours).
6. Rate of rewarming after therapeutic hypothermia.
7. First presenting cardiac rhythm (ventricular fibrillation OR pulseless ventricular tachycardia versus asystole OR pulseless electrical activity).

Meta-regression was not performed owing to the small number of included trials.

3.4.3.11 Sensitivity analysis

We planned to undertake sensitivity analysis between studies in which data were 'imputed' for ITT analysis, assuming that all missing participants experienced the event or that all missing participants did not experience the event.

3.4.3.12 Summary of findings table

We planned to use the principles of the GRADE system (Guyatt et al, 2008) to assess the quality of the body of evidence associated with specific outcomes:

1. best neurological outcome,

2. survival to intensive care discharge,
3. survival to hospital discharge,
4. survival up to six months,
5. long-term survival.

In our review we planned to construct a 'Summary of findings' (SoF) table using the GRADE software. The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence takes into consideration within study risk of bias (methodological quality), the directness of the evidence, heterogeneity of the data, precision of effect estimates and risk of publication bias.

3.5 RESULTS

3.5.1 Description of studies

Our sensitive search strategy resulted in 6068 hits by the database searches and 615 by other searches (Figure 3-1). Following removal of duplicates (2770), the remaining 3913 were screened. 3649 were excluded on reviewing title or abstract resulting in 264 for full paper review. The majority (188) were then excluded because they were not relevant or because the age of patients was outside the specified age for inclusion in this review (older than 24 hours of age and with a corrected gestational age of greater than or equal to 35 weeks, children and adolescents up to their 18th birthday). 54 on-going studies were excluded of which 38 only included adults greater than 18 years and 16 only included neonates less than 24 hours old. Finally, 18 studies were evaluated for inclusion and four ongoing paediatric RCTs (NCT00754481; NCT00797680; NCT00878644; NCT00880087).

After contacting experts about possible additional unpublished or on-going relevant studies, none were found (Appendix 9-3, p304). The chief investigators of the four ongoing paediatric RCTs were all contacted and confirmed that no result data were available.

There were no RCTs included from our systematic search of the medical databases.

The remaining 18 studies were all excluded for being non-randomised prospective (five) or retrospective (six) cohort studies, database registry studies (one), case studies (three), review (one), commentary (one), and protocol outline for future study (one). (See Table 3-2 Characteristics of excluded studies, for full description of all excluded studies).

The four ongoing RCTs may potentially be assessed in the future and fulfil this review's inclusion criteria (see Table 3-3 Characteristics on-going studies awaiting assessment).

Figure 3-1 PRISMA search flow diagram

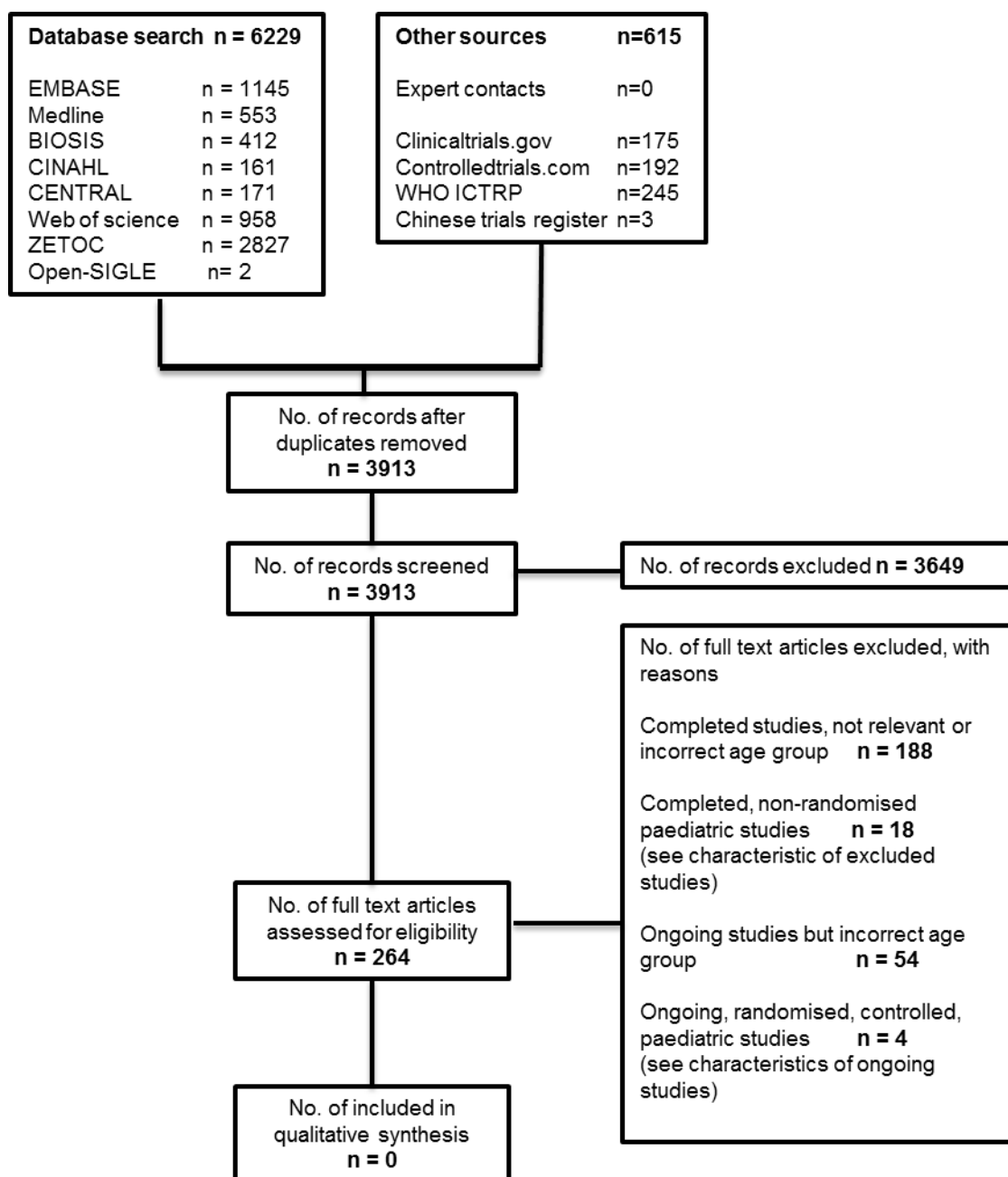


Table 3-2 Characteristic of excluded studies (ordered by study ID)

Study ID	Reasons for exclusion
Abend 2009	Non-randomised study Prospective, cohort study of paediatric post-cardiac arrest patients treated with therapeutic hypothermia receiving continuous electroencephalography. Single centre, March 2007 to September 2008. 14/19 (74%) survived, four with severe neurological morbidity. No comparative normothermia group.
Bembea 2010	Non-randomised study Database registry of in-hospital paediatric cardiac arrest patients (January 2005 to December 2007). Relationship of temperature in first 24 hours with survival and neurological outcome. 86/547 (16%) patients reported to have received; therapeutic hypothermia, extracorporeal membrane oxygenation or "ice-packs to head". No survival breakdown for this subgroup.
Buttram 2010 (abstract only)	Non-randomised study Prospective, cohort study comparing therapeutic hypothermia with normothermia after paediatric out-of-hospital cardiac arrest. Age 1 day to 18 years. 33/46 (77%) received therapeutic hypothermia. No difference in survival to hospital discharge between patients treated with hypothermia (39%) and standard therapy (23%), $p=0.49$.
Deasy 2010	Non-randomised study Retrospective, cohort study of paediatric out-of hospital cardiac arrest patients in Melbourne, Australia (Oct 1999 to 2007). Therapeutic hypothermia applied to 23/49 (46%) admitted to PICU with three survivors (OR 2.535, 95%CI [0.64-9.9], $p = 0.184$).
Doherty 2009	Non-randomised study Retrospective, cohort study comparing therapeutic hypothermia with normothermia over a two year period (September 2001 to August 2003) in five centres in Canada (4) and the UK (1). 29/79 (36.7%) received therapeutic hypothermia. 95% in-hospital cardiac arrest. Median duration of therapeutic hypothermia 20.8 hours (IQR 12-69 hours) at a mean temperature of $33.7 \pm 1.3^{\circ}\text{C}$. Hypothermia use was associated with higher mortality, more resuscitative interventions, higher post resuscitative lactate level and the use of ECMO. Non significant association between therapeutic hypothermia after adjustment for duration of cardiac arrest, use of ECMO and propensity score (Adjusted OR 1.99, 95% CI [0.45-8.85], $p=0.502$).
Fink 2010	Non-randomised study Retrospective, cohort study comparing therapeutic hypothermia with normothermia over a seven year period (July 2000 to August 2006) in a single centre (Pittsburgh, USA). 40/181 (22%) received therapeutic hypothermia. 55% in-hospital cardiac arrest. Median duration of therapeutic hypothermia 24.0 hours (IQR 16-48) at a median temperature of 34.0°C (33.5 - 34.8°C). No difference in hospital mortality; 55% therapeutic hypothermia group versus 55.3% standard therapy group ($p=1.0$). Hypothermia not associated with survival in univariate (OR 0.99, (95%CI [0.49-2.0]), $p=1.0$) or multivariate (OR 0.47 (95%CI [0.15-1.45], $p=0.2$) analysis.
Hein 2004	Case study
Kessler 2010	Non-randomised study Prospective, cohort study of paediatric post-cardiac arrest patients treated with therapeutic hypothermia (24 hours, 34°C) and monitored with electroencephalography. 21/35 (60%) patients survived. No comparative normothermia group.
Kobr 2011	Review

Study ID	Reasons for exclusion
Le Guen 2011	Non-randomised study Prospective, cohort study of extracorporeal support following out-of hospital refractory cardiac arrest. Inclusion of patients from 13 years to 70 years (Mean(SD) 45years (+-15)). All patients received therapeutic hypothermia. No breakdown of paediatric patient population.
Meert 2009	Non-randomised study Retrospective, cohort study of in-hospital cardiac arrest patients. Conducted in 15 centres in the USA over 18 months (July 2003-December 2004). Only 7/162 (4.1%) survivors and 8/181 (3.3%) non-survivors received therapeutic hypothermia.
Meert 2010	Comment
Moler 2009	Non-randomised study Retrospective, cohort study comparing in-hospital and out-of hospital paediatric cardiac patients in the USA over 18 months (July 2003 to December 2004). No outcome data for patients receiving or not receiving therapeutic hypothermia.
Moler 2011	Non-randomised study Retrospective, study of out-of-hospital cardiac arrest patients. Conducted in 15 centres in the USA over 18 months (July 2003 to December 2004). Only 1/53 (2%) survivors and 2/85 (2%) non-survivors received therapeutic hypothermia.
Sanada 1998	Case study
Silfvast 2003	Case study
Takeda 2009	Protocol for a randomised controlled trial of pharyngeal cooling system during cardiac arrest. Age inclusion 16 to 89 years.
Topjian 2011	Non-randomised study Prospective, intervention study of therapeutic hypothermia after paediatric cardiac arrest. Assessing the feasibility and safety of a standardized treatment protocol. Single centre, 6/12 (50%) of patients survived to discharge. No comparative normothermia group

ECMO: extracorporeal membrane oxygenation,

IQR: inter-quartile range

OR: odds ratio

CI: confidence interval

SD: standard deviation

Table 3-3 Characteristics of on-going studies (ordered by study ID)

Study Name	Method Design	Participants Age	Intervention 1 Treatment Duration Depth Rewarm	Outcomes 1 Primary	Notes
Contact	Phase	Cardiac arrest Definition		2 Secondary	
		Location	2 Treatment Duration Depth		
		Inclusion ^a			
<u>NCT00754481</u> Hypothermia for Cardiac Arrest in Paediatrics (HypCAP) Dr Jamie Hutchison, The Hospital for Sick Children, Toronto, Canada	Randomised, single blind (outcome assessor), parallel assignment efficacy Phase II study	≥ 38 weeks gestation up to and including 17 yrs Chest compressions ≥3 minutes In-hospital and out-of-hospital arrest GCS ≤ 10 at 1 hour post- cardiac arrest Invasive mechanical ventilation Randomised within six hours	1)Therapeutic hypothermia: 48 hours 33-34°C Rewarm 0.5°C every 2 hours to 36.5 °C 2)Therapeutic normothermia: 48 hours 36.5-37.5°C	1) Percentage of children achieving a "good outcome", (PCPC score of 1-3) at 12 months. 2) Cognitive and motor measures*, mortality (assessed at 1, 3, 6, and 12 months post-arrest), cerebral oedema*, adverse effects of hypothermia therapy* (* measured at 12 months post-arrest)	Planned enrolment 40. Study finished recruiting.
<u>NCT00797680</u> Duration of Hypothermia for Neuroprotection After Paediatric Cardiac Arrest Dr Ericka Fink Children's Hospital of Pittsburgh, Pennsylvania, USA	Randomised, open label, parallel assignment, safety and efficacy Phase II study	1 wk - 17 yrs. Chest compressions by a health care worker In-hospital and out-of-hospital arrest GCS ≤ 8 PICU physician decision to use therapeutic hypothermia. Central venous or arterial catheter in situ.	1) Therapeutic hypothermia: 72 hours 33 ± 1°C 2) Therapeutic hypothermia: 24 hours 33 ± 1°C	1) Degree of brain injury as measured by serum and urine biomarkers and Magnetic Resonance Spectroscopy at hospital discharge 2) Frequency of adverse events at 30 days	Planned enrolment 40. Planned end date April 2014

^aexclusion criteria not listed

GCS: Glasgow coma score

PCPC: Paediatric Cerebral Performance Category (Table 3-1)

Table 3-2 Characteristics of on-going studies (ordered by study ID) continued

Study Name	Method Design	Participants Age	Intervention 1 Treatment Duration Depth Rewarm	Outcomes 1 Primary	Notes
	Phase	Cardiac arrest Definition		2 Secondary	
		Location	2 Treatment Duration Depth		
		Inclusion ^a			
NCT00878644	Randomised, single blind (outcome assessor), parallel assignment, safety and efficacy	> 48 hours (with a corrected gestational age \geq 38 weeks) and < 18 years	1)Therapeutic hypothermia 48 hours 33° C \pm 1° C	1)Survival with good neurobehavioral outcome (assessed at 12months)	Planned enrolment 350.
Therapeutic Hypothermia to Improve Survival After Cardiac Arrest in Paediatric Patients-(THAPCA-OH) [Out of Hospital] Trial		chest compressions \geq 2 minutes	gradual re-warm to 36.75° C \pm 0.75°C maintained until 120 hours	2)Survival*, change in neurobehavioral function from pre-cardiac arrest to 12 months post-cardiac arrest, neuropsychological scores* (for participants who survive), neurological abnormality scores* (for participants who survive).	Planned study end date September 2015
Prof Frank W. Moler, University of Michigan, USA		out-of-hospital cardiac arrest only	2)Therapeutic normothermia 120 hours 36.75° C \pm 0.75°C	(*measured at 12months post arrest).	
NCT00880087	Randomised, single blind (outcome assessor), parallel assignment safety and efficacy	> 48 hours (with a corrected gestational age \geq 38 weeks) and < 18 years	1)Therapeutic hypothermia 48 hours 33° C \pm 1° C	1)Survival with good neurobehavioral outcome (assessed at 12months)	Planned enrolment 500.
Therapeutic Hypothermia to Improve Survival After Cardiac Arrest in Paediatric Patients-(THAPCA-IH) [In Hospital]) Trial		chest compressions \geq 2 minutes	gradual re-warm to 36.75° C \pm 0.75°C maintained until 120 hours	2)Survival*, change in neurobehavioral function from pre-cardiac arrest to 12 months post-cardiac arrest, neuropsychological scores* (for participants who survive), neurological abnormality scores* (for participants who survive).	Planned end date September 2015
Prof Frank W. Moler, University of Michigan, USA		in-hospital cardiac arrest only	2)Therapeutic normothermia 120 hours 36.75° C \pm 0.75°C	(*measured at 12months post arrest).	
	Phase III study	mechanical ventilation randomised within six hours			

^aexclusion criteria not listed

3.5.2 Risk of bias in included studies

No randomised controlled trials were identified. (see Table 3-2 Characteristics of excluded studies and Table 3-3 Characteristics of on-going studies)

3.5.3 Effects of interventions

No randomised controlled trials were identified. (see Table 3-2 Characteristics of excluded studies and Table 3-3 Characteristics of on-going studies)

3.6 DISCUSSION

3.6.1 Summary of main results

We found no high quality evidence, in the form of randomised or quasi-randomised controlled trials, for or against the use of therapeutic hypothermia in children after cardiac arrest.

3.6.1.1 *Excluded studies*

We excluded three cohort studies comparing the use of therapeutic hypothermia and normothermia or standard care in the paediatric population; two published (Fink et al, 2010; Doherty et al, 2009) and one in abstract form only (Buttram et al, 2009). A narrative review is given below.

Doherty et al (2009) retrospectively investigated the survival and neurological outcome of children by comparing the use of therapeutic hypothermia (n = 29) versus normothermia (n = 50). Included patients had predominantly suffered an IHCA (95%), often with associated chronic cardiac conditions (71%) and after surgery (59%). In patients with an a priori defined cardiac arrest duration of at least three minutes and who survived to 12 hours post return of spontaneous circulation, the use of therapeutic hypothermia was associated with increased 30 day mortality (unadjusted odds ratio (OR) [95% confidence interval (CI)] 2.5 [0.99 to 6.45]; P = 0.054), increased six month mortality (unadjusted OR [95% CI] 3.62 [1.37 to 9.62]; P = 0.009) and unfavourable neurological outcome (PCPC score 4 to 6) (unadjusted OR [95% CI] 2.92 [1.1 to 7.69]; P = 0.031). However, patients receiving therapeutic hypothermia were sicker due to a number of factors: longer duration of cardiac arrest, more pharmacological interventions during resuscitation, greater post-resuscitation serum lactate levels, higher multi-organ dysfunction score and more renal replacement therapies. More patients receiving therapeutic hypothermia also received extracorporeal life support. When logistic regression modelling was performed to account for these confounding factors, the use of therapeutic hypothermia did not statistically increase the risk of 30 day mortality (adjusted OR [95% CI] 2.5 [0.55 to 11.49] P = 0.238), six month mortality (adjusted OR [95%

CI] 1.99 [0.45 to 8.85] $P = 0.502$) or unfavourable neurological outcome (adjusted OR [95% CI] 2.0 [0.45 to 9.01] $P = 0.364$).

Fink et al (2010) in a single centre, retrospective study also showed no significant difference in mortality and gross neurological outcomes for patients treated with either therapeutic hypothermia or normothermia after cardiac arrest. The patient population differed from the study by Doherty et al (2009) and IHCA (55%) and OHCA (45%) patients with predominately an asphyxial aetiology (91%) causing the arrest. Excluded from the population were all patients with congenital heart disease. Patients received either therapeutic hypothermia ($n = 40$) or standard normothermia therapy ($n = 141$). Similar to Doherty et al (2009), patients receiving therapeutic hypothermia had a longer duration of cardiac arrest, more doses of epinephrine and fewer were witnessed arrests and therefore had an increased baseline risk of mortality. In patients who were normothermic at the start of therapy, therapeutic hypothermia target temperature was reached within a median 8 hours [IQR 5 to 7]. Mortality at hospital discharge was similar for patients receiving therapeutic hypothermia (55.0%) and standard therapy (55.3%; $P = 1.0$). Therapeutic hypothermia was not associated with survival (adjusted OR [95% CI] for mortality; 0.47 [0.15 to 1.45]; $P = 1.0$). This study also reported no difference in proportion of survivors discharged home after therapeutic hypothermia (78%) versus standard therapy (68%; $P = 0.46$).

The third study was only available in abridged abstract form (Buttram et al, 2009). This prospective study compared therapeutic hypothermia ($n = 33$) and standard therapy ($n = 13$) in paediatric patients surviving to PICU admission after IHCA and OHCA. Mortality at hospital discharge was not significantly different (therapeutic hypothermia: 61%, versus standard therapy: 77%, $P = 0.49$). However, no data is presented to compare the demographics of the two groups.

These three excluded studies were unable to demonstrate a significant difference in survival or good neurological outcome at various time points after the use of therapeutic hypothermia compared with normothermia. Methodological problems including the non-randomised design of the studies are a significant problem. In both Doherty et al (2009) and Fink et al (2010), therapeutic hypothermia was used in patients already at higher risk of mortality with

associated risk factors known to exist after paediatric cardiac arrest. In addition, it is difficult to compare these two studies owing to significant differences in patient demographics between each study. The high proportion of IHCA patients with chronic cardiac conditions in the Doherty et al (2009) study will have had an increased chance of survival compared with the higher proportion of asphyxial arrest patients and OHCA patients in Fink et al (2010).

These studies do focus on important safety issues regarding the use of therapeutic hypothermia which can usefully inform further prospective randomised studies. Excess hypothermia (defined as core temperature less than 32°C) was only reported in patients receiving therapeutic hypothermia and occurred in 17.2% (Doherty et al 2009) and 15% (Fink et al 2010) of patients. Fink et al (2010) identified that excess hypothermia was associated with increased mortality in this group. Hyperthermia (defined as temperature greater than 38°C) in post cardiac arrest patients is known to increase mortality and neurological injury (Bembea et al, 2010) and international recommendations advocate avoidance (Kleinman et al, 2010). However, it occurred in 38% of standard therapy and 17% of therapeutic hypothermia treated patients although was not associated with increased mortality in this study (Fink et al, 2010). Neither Doherty et al (2009) or Fink et al (2010) reported an increase in post cardiac arrest infections, arrhythmias or bleeding, in patients receiving therapeutic hypothermia. Therefore, a randomised controlled trial treatment protocol will need to actively avoid inadvertent hypothermia and hyperthermia in both the therapeutic hypothermia group and normothermia group and continue to monitor for potential adverse effects of therapeutic hypothermia.

We excluded two prospective, non-randomised studies on paediatric patients after cardiac arrest who all received therapeutic hypothermia and where there was no comparison group (Topjian et al, 2011; Abend et al, 2009). We excluded an additional three retrospective, non-randomised studies of paediatric patients after cardiac arrest where factors associated with survival were reported. Deasy et al reported that 23/46 (46%) of patients admitted to PICU after cardiac arrest were treated with therapeutic hypothermia. However, its use was not associated with survival (unadjusted OR [95%CI] 2.54 [0.64 to 9.9]; $P = 0.184$). Two retrospective studies of in-hospital cardiac arrest (Meert et al, 2009) and out-of-hospital

cardiac arrest (Moler et al, 2011) separately reported proportion of patients receiving therapeutic hypothermia, although the proportions were so small (4% and 2% respectively) that comparison between groups was inappropriate.

3.6.1.2 On-going studies

We found four on-going studies (NCT00754481; NCT00797680; NCT00878644; NCT00880087). Two phase III studies (NCT00878644; NCT00880087) using therapeutic hypothermia (32 to 34°C) for 48 hours with gradual rewarming and further control of temperature to normothermia (36.0 to 37.5°C) for a further three days are comparing children after in-hospital cardiac arrest with out-of hospital arrest. These two studies are designed to detect a difference in survival with good neurological outcome at 12 months. One phase II (pilot) study (NCT00754481) is comparing therapeutic hypothermia (33 to 34°C) for 48 hours with gradual rewarming to normothermia (36.5 to 37.5°C); and a fourth phase II (pilot) study (NCT00797680) is comparing 24 versus 72 hours of therapeutic hypothermia (32 to 34°C) with gradual rewarming.

All four studies are using a similar therapeutic hypothermia target temperature ($33^{\circ}\text{C} \pm 1^{\circ}\text{C}$) which is the target temperature demonstrated to be efficacious in neonatal and adult RCTs. Three studies will maintain target temperature for 48 hours and compare with a therapeutic active normothermia group (NCT00754481; NCT00878644; NCT00880087). The use of an actively controlled normothermia group aims to eliminate the confounding effect of hyperthermia (temperature greater than 38°C) in the control group. This was noted in the adult, European hypothermia after cardiac arrest trial (HACA, 2002) with approximately 25% of the patients in the control group experiencing hyperthermia and potentially increasing their risk of neurological injury (HACA, 2002).

Duration of therapy may be an important variable. The fourth study is comparing 24 and 72 hours of therapeutic hypothermia (NCT00797680). The other three studies are using 48 hours of therapeutic hypothermia as the treatment duration. This compares with the two adult studies which used 12 hours (Bernard et al, 2002) and 24 hours (HACA, 2002) of therapy and the neonatal trials which used 72 hours of therapy (Jacobs et al, 2007;

Azzopardi et al, 2009). Despite the wide variation in duration of therapy between studies, beneficial effects were still seen and therefore further investigation of this treatment variable is important. The advantages of a longer duration of therapy include the potential for greater beneficial effect from the intervention and this is supported in experimental animal studies, particularly with an increased delay from return of spontaneous circulation to commencement of therapy (Clark et al, 2008; Colbourne et al, 1999). However, prolonged duration may increase the risk of infection and associated morbidity. The increased duration may also have greater financial implications associated with prolonged ventilation and a longer stay in PICU which should be taken into account.

Important functional and neurological outcomes are being assessed in all on-going studies. The use of the simple functional outcome scores (e.g. Paediatric Cerebral Performance Category (PCPC) (Fiser, 1992)) will give some useful information regarding crude functioning. The PCPC score was designed and validated in the post-cardiac arrest population but will not be able to demonstrate subtle functional and developmental problems. The use of multiple, in-depth neurodevelopmental and neuropsychological tests, as planned in two studies, will hopefully give a much clearer and more accurate assessment of subtle effects of therapeutic hypothermia at different stages of brain development (NCT00878644; NCT00880087). Biomarkers (serological and radiological) are also a potential tool in early prediction of short term survival and also levels of developmental outcome over a longer term (NCT00797680).

In a future Cochrane systematic review we hope to assess these four studies together with any additional randomised controlled studies and to perform a meta-analysis as detailed above. In addition, we will use individual patient data if possible.

3.6.2 Overall completeness and applicability of evidence

Currently the available evidence neither supports nor refutes the use of therapeutic hypothermia in the paediatric population. However this lack of evidence justifies further randomised controlled trials and the encouragement of researchers and clinicians to continue investigation of this therapy. The on-going studies will hopefully provide valuable

information regarding this therapy and be available for future systematic assessment, as described in this review.

3.6.3 Quality of the evidence

We found no high quality evidence for or against the use of therapeutic hypothermia in children after cardiac arrest. Formal quality assessment and meta-analysis of non-randomised studies was not performed (Stroup, 2000).

3.6.4 Potential biases in the review process

We undertook a systematic search for evidence using a sensitive search strategy as described in Section 6.4 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins JPT et al, 2011) to find randomised controlled trials, in order to limit the risk of missing published studies. Contacting experts in paediatric critical care and hypothermia research did not uncover further studies and confirmed that the on-going studies identified were either still recruiting or undergoing analysis. The possibility of additional un-published randomised controlled trials does exist, although we feel this is small.

Non-randomised trials have been discussed in this review owing to the absence of high quality randomised controlled trials. However, owing to the design of the systematic search focusing on randomised studies there is a possibility of missing non-randomised studies. Experts were asked for any additional published or unpublished non-randomised studies and as no additional studies were identified this possibility is also small.

3.6.5 Agreements and disagreements with other studies or reviews

The use of therapeutic hypothermia in children after cardiac arrest is outlined in the international liaison committee on resuscitation (ILCOR) guidance (Kleinman et al, 2010). The use of therapeutic hypothermia (32-34°C) *may be beneficial* in adolescent children presenting in ventricular fibrillation cardiac arrest. In infants and children who remain comatose after resuscitation from paediatric cardiac arrest, therapeutic hypothermia (32-34°C) *may be considered*.

Support for these recommendations is extrapolated from the neonatal evidence of 72 hours of therapeutic hypothermia after hypoxic ischaemic encephalopathy within six hours of birth (Jacobs et al, 2007; Azzopardi et al, 2009) and the two RCTs of 12 to 24 hours of therapeutic hypothermia in adults after ventricular fibrillation cardiac arrest (Bernard et al, 2002; HACA, 2002). The findings and limitations of the two retrospective cohort studies ((Doherty et al, 2009; Fink et al, 2010) and the lack of paediatric high quality evidence are acknowledged. The recommendations are given with the caution that the benefits or harm of therapeutic hypothermia in this population is not known.

We found no further published randomised or non-randomised paediatric studies since the publication of the ILCOR guidelines. Reassessment of the paediatric recommendations will be necessary when the on-going studies identified in this review have been completed.

3.6.6 Limitations of review

The main limitation of this review is the *a priori* exclusion of non-randomised controlled studies at the protocol stage, which results in no evidence being formally analysed. The Cochrane Collaboration principles regarding systematic reviews ensure 'the conduct is a reliable synthesis of available evidence on a given topic and that the science is cumulative and facilitates decisions considering all the evidence of an intervention' (Higgins JPT et al, 2011). This systematic review has adhered to these principles with the opportunities to review and revise in the future. However, a restriction that the Cochrane Anaesthesia Review Group set out after reviewing the proposal for this systematic review was the *a priori* inclusion of only randomised and quasi-randomised controlled trials in the study protocol.

The formal use of non-randomised trials in systematic review has been detailed by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group (Stroup, 2000). The methodological design weaknesses present in observational studies (e.g. lack of blinding and risk of exposure being linked to a hidden confounder) and the risks of heterogeneity of studies can be amplified in a meta-analysis. One solution is to choose the correct statistical tests to assess this (Trinquart & Touzé, 2009). However, the scientific rigour regarding analysis of included studies, including assessment of bias and heterogeneity is less well

validated than for randomised controlled trials (Wells et al, 2010). Conversely, Shrier et al (2007) argues that well designed observational studies with appropriate assessment of confounding variables can be included in meta-analysis and give examples where results are comparable to meta-analysis of randomised controlled trials only and in some situation (i.e. where the number of RCTs are limited or of small size) produce more accurate results. They would advocate that non-randomised controlled studies should only be excluded after systematic assessment of the study and not *a priori* at the design stage, as was performed in this review. Unfortunately, in the context of this review, the major risk factor of combining observational studies is present in the two identified published studies by Fink et al (2010) and Doherty et al (2009). The high probability of 'confounding by indication' (defined as: when a treatment is specifically provided to a subject because of their probability of experiencing the outcome) (Shrier et al, 2007) as demonstrated through the use of therapeutic hypothermia in more severely affected children post cardiac arrest is present and risks limiting the strength of the observational findings. Adjustment of confounders at the design stage (i.e. inclusion of more severely affected patients) or at the analysis stage (by the use of multiple regression analysis or propensity scores) (Greenland et al, 1999) are appropriate methodological techniques for limiting this effect. Although, in the context of the two studies, even with appropriate statistical adjustments, too many additional limitations exist (e.g. the small sample sizes and heterogeneous populations) resulting in a lack of confidence in the final outcome findings.

As detailed in the results, no randomised controlled trials were found, therefore creating what Cochrane define as an 'empty review'. This can lead to controversy with variability in publication of the review and ambiguity surrounding the presentation and reporting of excluded evidence (Montgomery et al, 2011). The publication of this review is justified on the grounds that the clinical question is important for practice or policy. Trials are feasible (as demonstrated by the on-going studies) although there may need to be amendment to the protocol as part of an iterative process in the future. A recent analysis of the Cochrane library discovered 376 empty reviews (8.7% of all active reviews) (Montgomery et al, 2011). However, they typically contained few, if any on-going studies (0.14 per review (SD 0.49)).

The four on-going randomised controlled trials identified in this review are therefore an exception to the norm and this review may only be 'empty' temporarily.

There is no guidance from Cochrane on the reporting of empty studies, particularly the section on *implications for practice*. Issues have arisen regarding frustration expressed by policy-makers on finding no evidence after searching for the guidance in the Cochrane library. One approach proposed by Lang et al (2007) suggests that authors of empty reviews note observations based on excluded studies so that decision-makers are not left empty handed. However, basing conclusions on studies which do not meet inclusion criteria increases the risk of bias (Montgomery et al, 2011). The position of not basing conclusions on the non-randomised studies has been taken here especially in anticipation of randomised controlled trial evidence becoming available in the future.

3.7 CONCLUSION

3.7.1 Implications for practice

We found no randomised controlled studies, so this review concludes that there is no evidence of effect of therapeutic hypothermia in paediatric cardiac arrest rather than evidence of no effect. We therefore can neither give a recommendation for or against the use of therapeutic hypothermia in clinical practice. Current guidance from the International Liaison Committee on Resuscitation recommends consideration of therapeutic hypothermia in infants and children and that its use may be beneficial in adolescents with ventricular fibrillation cardiac arrest (Kleinman et al, 2010). These recommendations are extrapolated from neonatal and adult clinical trials. Further research in the paediatric population is needed to confirm these recommendations.

3.7.2 Implications for research

More studies are needed to investigate the use of therapeutic hypothermia after paediatric cardiac arrest. Continued support for the on-going in-hospital and out-of-hospital cardiac arrest studies identified in this review and future studies is essential to enable assessment of any effect of therapeutic hypothermia in the paediatric population (NCT00754481; NCT00797680; NCT00878644; NCT00880087). The important differences which exist in cardiac arrest aetiology and neurological development in the paediatric population compared with the studied neonatal and adult populations support this.

Adequately sized studies will be required to investigate the effect of therapeutic hypothermia and to define the duration, temperature depth and rewarming rates during administration. It is likely that international collaboration will be required to recruit sufficient numbers of patients to ensure adequately powered studies and findings are generally applicable.

Table 3-4 Chapter 3 and RCT feasibility

What have we learnt from this study towards the feasibility of a UK randomised controlled trial?

Confirmation that there are currently no published randomised controlled trial data examining therapeutic hypothermia as a neuroprotection therapy in children after cardiac arrest.

Paediatric randomised controlled trials are on-going, successfully funded and recruiting, although only in North America and Canada.

Future meta-analysis (with individual patient data) may be possible in five to seven years.

Communication with international experts across the world through this review process has revealed a willingness to advise upon, participate in, and support a UK randomised controlled trial of therapeutic hypothermia after paediatric cardiac arrest.

3.8 ACKNOWLEDGEMENT

We would like to thank Jane Cracknell and Karen Hovhannisyan from the Cochrane Anaesthetic Review Group for their help and editorial advice during the preparation of this review. We would also like to thank Mathew Zacharias (content editor), Nathan Pace (statistical editor), Jasmin Arrich, Alexis Topjian and Ronan O'Sullivan (peer reviewers) for their help and editorial advice during the preparation of this protocol for the systematic review.

3.9 CONTRIBUTORSHIP

Conceiving the review: Barnaby Scholefield (BS), Heather Duncan (HD), Kevin Morris (KM)

Co-ordinating the review: BS

Undertaking manual searches: BS, HD, KM

Screening search results: BS, HD, KM

Organizing retrieval of papers: BS

Screening retrieved papers against inclusion criteria: BS, HD, KM

Appraising quality of papers: BS, HD, KM

Abstracting data from papers: BS, HD, KM

Writing to authors of papers for additional information: BS

Providing additional data about papers: BS

Obtaining and screening data on unpublished studies: BS, HD, KM

Data management for the review: BS

Interpretation of data: BS, HD, KM, Khalid Khan (KK), Fang Gao-Smith (FGS)

Statistical inferences: BS, PD, KK, FGS

Writing the review: BS, HD, KM

Performing previous work that was the foundation of the present study: BS

Guarantor for the review (one author): BS

Person responsible for reading and checking review before submission: KM

4 Current practice of targeted temperature management and future trial acceptability

"New opinions are always suspected, and usually opposed, without any other reason but because they are not already common."

John Locke (English philosopher born 1632).

This chapter has been *published* in two papers

B.R.Scholefield, H.P. Duncan, and K.P. Morris, Survey of the use of therapeutic hypothermia post cardiac arrest. *Arch Dis Child*, 2010. 95(10): p. 796-9. (Appendix 9.7, p322)

B.R.Scholefield, M. Lyttle, K.Berry, H.P. Duncan, and K.P. Morris, Survey of the use of therapeutic hypothermia after cardiac arrest in UK paediatric Emergency Departments. *Emerg Med J* Published Online First: 2 March 2012
doi:10.1136/emered-2011-200348 (Appendix 9.8, p326)

4.1 ABSTRACT

4.1.1 Introduction

International resuscitation guidelines recommend consideration of post paediatric cardiac arrest therapeutic hypothermia based upon supportive evidence from adult and neonatal studies. However, the lack of paediatric evidence may limit the implementation of these guidelines in practice. Current UK practice of temperature management after resuscitation in the Paediatric Emergency Department and the Paediatric Intensive Care Unit is not known. Knowledge of current practice is essential to assess the feasibility of introducing further research in this area and to inform trial design.

4.1.2 Aims

To ascertain current practice of post cardiac arrest temperature management in UK Paediatric Intensive Care Units and Paediatric Emergency Departments, and to assess attitudes and opinions of further research in this area.

4.1.3 Methods

Two anonymous web-based surveys. Survey one: All UK paediatric intensive care (PIC) consultants (n=149). Survey two: A selective sample of UK paediatric emergency medicine consultants (n=77) from 28 UK Emergency Departments.

4.1.4 Results

Survey one: 113/149 (76%) of PIC consultants surveys were returned. 65% (73/113) responded that they do not know if therapeutic hypothermia improves survival after cardiac arrest. Despite this 48% (54/113) 'always' or 'often' use therapeutic hypothermia after return of spontaneous circulation following cardiac arrest in children. Amongst those who rarely or never use therapeutic hypothermia the commonest explanation given was 'not enough research evidence' (91% 54/59). With respect to the dose of therapeutic hypothermia the median duration of cooling used is 24-48 hours (range 4-72 hours) and median target temperature 34-35 °C (range 32 to 37°C).

Survey two: 62% (48/77) of surveyed paediatric emergency medicine consultants responded from 75% (21/28) of Emergency Departments. 90% (43/48) were aware of the literature concerning therapeutic hypothermia after cardiac arrest in adults. However, 63% (30/48) had never used therapeutic hypothermia in paediatric practice. All departments had at least one method of inducing therapeutic hypothermia (surface cooling; air/water blankets; intravenous cold fluid or catheters). Reasons stated for not inducing therapeutic hypothermia included no equipment available (26%; 11/42), therapeutic hypothermia not advocated by the local PICU (24%; 10/42) and not enough evidence for its use (24%; 10/42). Therapeutic hypothermia was considered based on advice from the local PICU (68%; 17/25) or likelihood of recovery after arrest (32%; 8/25).

Both surveys reported support for a UK RCT of therapeutic hypothermia versus normothermia, an RCT being ethical and accepted the utilisation of deferred consent.

4.1.5 Conclusions

Wide variation in UK paediatric intensive care and paediatric emergency medicine practice in the use of therapeutic hypothermia and a state of clinical equipoise is demonstrated by these two surveys which show important support for UK multi-centre collaboration in a future trial of therapeutic hypothermia after cardiac arrest. The support would potentially enable early induction of therapeutic hypothermia in UK Emergency Departments during a UK RCT of therapeutic hypothermia after paediatric cardiac arrest.

4.2 INTRODUCTION

In the UK children sustaining an out of hospital cardiac arrest are managed by teams led by emergency medicine consultants, often in collaboration with paediatric intensive care consultants. The decision whether to use targeted temperature control and initiate therapeutic hypothermia is therefore made by these two groups, informed by their understanding of the research evidence, clinical guidelines, institutional practices, experience and personal clinical knowledge. They are therefore an ideal source to assess current practice and to ascertain whether clinical equipoise exists regarding the use of therapeutic hypothermia after paediatric cardiac arrest.

Clinical equipoise has been defined as *'there existing an honest, professional disagreement among expert clinicians about the preferred treatment'* (Freedman, 1987). Without clinical equipoise randomisation of patients into an RCT to compare two treatments (where the body of belief is that one therapy is more efficacious than the other) is unethical (Freedman, 1987). In addition, research resource limitations in the health service require prioritisation of resources. Clinicians are best placed to clarify the importance of a clinical question in relation to other clinical needs.

4.2.1 Current Guidance

Therapeutic hypothermia (TH) induced to $33\pm1^{\circ}\text{C}$ after ventricular fibrillation associated cardiac arrest in adults and hypoxic-ischaemic encephalopathy in neonates has been shown to significantly improve neurological outcomes (Bernard et al, 2002; Gluckman et al, 2005; HACA, 2002; Azzopardi et al, 2009; Shankaran et al, 2005). Whether the same benefit can be achieved after paediatric cardiac arrest is not yet known, although the International Liaison Committee for Resuscitation (ILCOR) recommend 'considering the use of TH for 12-24 hours in infants and children who remain comatose after resuscitation' (ILCOR, 2006).

An anonymous web based survey conducted in North America highlighted wide variation of practice in paediatric intensive care units concerning when therapeutic hypothermia is

started and how it is administered (Haque et al, 2006). As this survey was undertaken some years ago with little input from UK paediatric intensivists and a poor overall response rate (12%) it does not provide an accurate picture of current UK practice.

4.2.2 Narrow therapeutic window

Animal studies indicate that there is a narrow therapeutic window for TH, and early treatment appears more efficacious in preventing severe hypoxic-ischaemic injury after cardiac arrest (Colbourne & Corbett, 1995; Markarian et al, 1996; Kuboyama et al, 1993; Iwata et al, 2007). Adult and neonatal studies showing neurological benefit have recruited patients to receive TH within six hours of cardiac arrest or hypoxic injury (Bernard et al, 2002; Shankaran et al, 2005; HACA, 2002; Azzopardi et al, 2009; Gluckman et al, 2005). Whether the same therapeutic window applies to paediatric patients following cardiac arrest is as yet unknown.

Paediatric patients resuscitated after cardiac arrest are cared for in Paediatric Intensive Care Units (PICUs). With the centralisation of PICUs, these children often require transfer from the presenting Emergency Department to a regional PICU, in a different hospital (Pearson et al, 2001). Owing to logistical delays in transportation, it may be necessary for TH to be commenced in the Emergency Department in order to effectively deliver treatment within the narrow therapeutic window.

This chapter therefore aims to address the questions of should we and could we undertake an RCT in the UK by ascertaining current practice in UK Emergency Departments and PICUs, asking whether clinical equipoise exists amongst medical staff, and investigating their willingness to participate in a UK RCT.

4.3 AIMS

4.3.1 Primary Aim

1. To ascertain current practice amongst paediatric intensive care and emergency department physicians regarding the use of TH after paediatric cardiac arrest.

4.3.2 Secondary Aims

1. Assess if clinical equipoise exists regarding the use of therapeutic hypothermia after cardiac arrest.
2. Establish whether there is support for a future randomised control trial.

4.4 METHODOLOGY

4.4.1 Setting and participants

Survey one: 149 PIC consultants from 25 UK PICUs were identified by contacting all NHS PICUs in the UK.

Survey two: 77 emergency medicine Consultants from 28 UK Emergency Departments were invited to participate by selecting known members of the Association of Paediatric Emergency Medicine. Half were from tertiary children's hospitals which have PICU on-site and see only children within their emergency department, the remainder were from secondary general hospitals which have no PICU on-site and see a mix of adults and children within their emergency departments. For the purposes of this study we use the term emergency medicine consultants to refer to all consultants who participated in survey two.

4.4.2 Study Design

Survey one and two: Relevant questions were generated by the study group and piloted on a group of ten PIC consultants (survey one) and eight emergency medicine consultants (survey two) from three different hospitals for further feedback and hyperlink access testing.

Survey one: To maximise response rates, as recommended in the Tailored Design Method for surveys (Dillman DA, 2007), a personal invitation to participate was sent out on October 1st 2008. Weblinks to the survey were sent out via email three further times and the internet link was closed on the 23rd November 2008. Survey two: An invitation to participate was sent on the 1st April 2010. Invitations were sent three further times and the internet link was closed on the 30th June 2010. Survey questions are shown in appendix 9.5 & 9.6 (p314). Both surveys were created using Microsoft ASP.NET 2008 (Microsoft, Seattle, WA).

4.4.3 Data collection

Data was collected electronically and imported into Microsoft Excel (Microsoft, Seattle, WA). Responders were identified by a unique code; this ensured that email reminders were only sent to non-responders.

4.4.4 Statistical Analysis

Microsoft Excel (Microsoft, Seattle, WA) was used for data analysis and results are presented as percent of survey responders, or mean (standard deviation). Agreement was defined as percentage responding 'agree' or 'strongly agree' from a five point Likert scale (strongly agree, agree, neutral, disagree and strongly disagree). An inter-rater agreement score was calculated for responses from emergency medicine consultants from the same Emergency Department.

4.4.5 Ethics

This study was reviewed by Birmingham Children's Hospital research and development department who categorised it as clinical evaluation involving NHS clinical staff (Paediatric Intensive Care and Emergency Medicine Consultants) and evaluating practice within their professional role. Therefore, Regional Ethics Committee waived requirement for approval. Formal advice has recently been published by the National Research Ethics advisory Service confirming this as a widely accepted decision (National Research Ethics Service, 2011).

4.5 RESULTS

4.5.1 Survey one

Of 149 consultants surveyed 113 responses (76%) were received. Consultants responded to questions about their current use of therapeutic hypothermia (Table 4-1), how they select patients (Table 4-2), what 'dose' of hypothermia they use (Figure 4-1), methods of cooling (Table 4-3) and their views on further research (Table 4-4).

4.5.2 Use of therapeutic hypothermia

65% (73/113) reported not knowing if therapeutic hypothermia after cardiac arrest improves survival. 48% (54/113) always or often use therapeutic hypothermia with the remaining 52% (59/113) stating they seldom or never use it. The commonest reason given by those who seldom or never use hypothermia was 'not enough research evidence' (91%; 54/59).

4.5.3 Patient selection

65% (51/78) of PIC consultants who have used therapeutic hypothermia would not change their practice according to whether the cardiac arrest occurred in or out of hospital.

The time to return of spontaneous circulation (ROSC) after cardiac arrest was influential in decision making for 66% (50/76) (Table 4-2). A higher proportion would commence therapeutic hypothermia for ROSC times between 5 and 30 minutes, though 23% (17/76) would even consider therapeutic hypothermia for a ROSC delay exceeding 60 minutes.

Table 4-1 Use of therapeutic hypothermia (survey one)

	n	Yes n(%)	No n(%)	Don't know n(%)		
Do you believe that therapeutic hypothermia improves survival after cardiac arrest in children?	113	29 (26)	11 (10)	73 (65)		
Does your clinical practice change if the child has an in-hospital cardiac arrest rather than an out-of hospital cardiac arrest?	78 ^a	27 (35)	51 (65)			
		Never n (%)	Seldom n (%)	Often n (%)	Always n (%)	% Often or Always
Do you use induced hypothermia as a therapy after resuscitation from cardiac arrest in children who have a return of spontaneous circulation?	113	37 (33)	22 (19)	44 (39)	10 (9)	48
Do you induce hypothermia as a therapy after in-hospital cardiac arrest in children?	77 ^a	1 (1)	30 (39)	36 (47)	10 (13)	60
Do you induce hypothermia as a therapy after out-of-hospital cardiac arrest in children?	76 ^a	4 (5)	19 (25)	35 (46)	18 (24)	70

^a response from those who 'always', 'often' or 'seldom' use therapeutic hypothermia only

Table 4-2 Patient selection and dose of hypothermia (survey one)

	n	Yes n (%)	No n (%)	Don't know n (%)
Which [if any] of the following influences your current use of hypothermia as a therapy after cardiac arrest? [you can select more than one]				
Return of spontaneous circulation	76 ^a	50 (66)	21 (28)	5 (7)
Delayed opportunity to cool	74 ^a	22 (30)	42 (57)	10 (14)
Witnessing arrest	76 ^a	21 (28)	46 (61)	9 (12)
Pupillary reaction	74	20 (27)	46 (62)	8 (11)
Age	76 ^a	2 (3)	68 (90)	6 (8)
Does your unit have a specific protocol for implementing hypothermia therapy?	76	5 (7)	69 (90)	2 (3)
Where would you actively start to induce hypothermia in your patients?				
Emergency Department	73	24 (33)	49 (67)	
Referring hospital	74	34 (46)	40 (54)	
Intensive care unit	77	77(100)	0 (0)	
Do you have a fixed length of time [as opposed to variable length] you would routinely maintain hypothermia?	75	33 (44)	42 (56)	
Do you control the speed of rewarming?	76	38 (50)	38 (50)	
Do you use active rewarming devices?	77	19 (25)	58 (75)	

^a percent total greater than 100 due to rounding.

4.5.4 Methods of inducing and maintaining therapeutic hypothermia

90% (69/76) of PIC consultants do not have a protocol for the use of therapeutic hypothermia in their unit.

Various combinations of cooling methods were reported, with a circulating water blanket the most commonly used (78%; 59/76) (Table 4-3).

Table 4-3 Method of inducing therapeutic hypothermia (survey one)

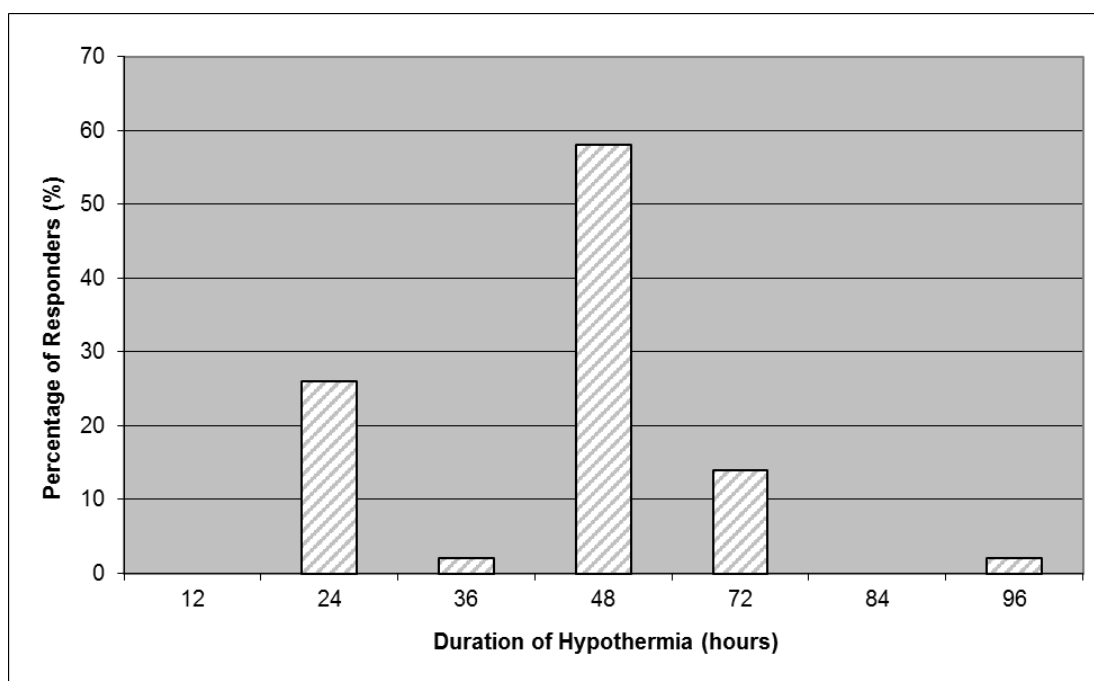
Method of Cooling	n (%) ^a
Water blanket	59 (78)
Ice packs to skin	47 (62)
Air blanket	32 (42)
Intravascular cooling device	6 (8)
Wet linen	4 (5)
Intravenous ice-cold (4°C) saline	4 (5)

4.5.5 'Dose' of hypothermia

Duration: The stated duration of induced hypothermia ranged from 4 to 96 hours. The maximum duration of cooling used is shown in Figure 4-1. The majority cool for a duration of up to 24-48 hours (85%; 65/76) with 15% (11/76) having a maximum cooling time longer than 48 hours.

Depth of cooling ranged from 32-37 °C with only 33% (25/76) targeting 33±1°C (Figure 2). The two responders (3%) who stated 36-37°C commented that they use cooling methods to actively avoid hyperthermia rather than to induce hypothermia.

Speed of rewarming is controlled by 50% (38/76) of responders with a range of 0.1-1.0°C/hour given as the target temperature increase.

Figure 4-1 Maximum stated duration of therapeutic hypothermia used (n=65)

4.5.6 Views on future research into therapeutic hypothermia

There continues to be a state of clinical equipoise in the UK regarding the use of therapeutic hypothermia after cardiac arrest according to 73% (82/113) of PIC consultants.

86% (97/113) would randomise their patients into a RCT of therapeutic hypothermia in cardiac arrest. There was greatest support for a comparative trial of hypothermia versus normothermia. There was strong support for a randomised controlled trial of therapeutic hypothermia being ethical (89%; 101/113), and utilising deferred consent (85%; 96/113).

Although 83% (94/113) of those surveyed felt that publication of a large multi-centre study undertaken in the United States would inform them of the benefit or lack of benefit of therapeutic hypothermia to their own patient population, 47% (53/113) agree that a UK trial is needed in addition to a US trial.

Table 4-4 Opinions regarding current and further research (survey one)

Statement	n	Agreement † n (%)	Mean‡	SD
The publication of a large randomised controlled trial currently being designed in the USA in the use of hypothermia in children after cardiac arrest would convince me of the benefit or lack of benefit for its use in my patient population	112	93 (83)	3.9	± 0.6
A multi-centre randomised controlled trial conducted in the United Kingdom in the use of hypothermia in children after cardiac arrest is necessary in addition to a USA study to convince me of its use in my patient population	113	53 (47)	3.2	±1.1
I currently feel there is clinical equipoise regarding the use of hypothermia versus normothermia after cardiac arrest in children.	113	82 (73)	3.8	± 0.8
It is ethical to perform a randomised controlled trial of hypothermia therapy in children after cardiac arrest	111	99 (89)	4.2	± 0.9
It is ethical to use deferred consent in clinical trials investigating therapies immediately after cardiac arrest	113	99 (88)	4.1	± 0.9

† Agreement = percentage responding 'agree' or 'strongly agree'

‡ Mean score on a Likert scale: 5 (strongly agree), 4 (agree), 3 (neutral), 2 (disagree) and 1 (strongly disagree)

*SD = standard deviation

4.5.7 Survey two

Of 77 emergency medicine consultants surveyed, 62% (48/77) responded. 75% (36/48) were consultants solely in Paediatric Emergency Medicine, and 25% (12/48) held dual accreditation in Adult and Paediatric Emergency Medicine. Responses were from 75% (21/28) of Emergency Departments. Ten Emergency Departments were located in tertiary children's hospitals which only see children. Eleven were located in secondary general hospitals where consultants manage both adult and paediatric patients.

Consultants responded to questions about their current use of TH (Table 4-5), how they select patients (Table 4-6), methods of cooling available (Table 4-7) and their views on further research (Table 4-8).

Table 4-5 Use of therapeutic hypothermia (survey two)

Question	n	Yes n (%)	No n (%)	Don't know n (%)		
Do you look after children post-cardiac arrest in ED?	48	48(100)	0	0		
Are you aware of published research regarding TH in adults post-cardiac arrest?	48	43 (90)	5 (10)	0		
Do you have a TH protocol for adults?	46 ^a	8 (17)	25 (52)	13 (27)		
Do you have a TH protocol for children?	47	0	46 (98)	1 (2)		
Do you believe TH improves outcome after paediatric cardiac arrest?	47	5 (11)	0	42 (89)		
	n	Always n (%)	Often n (%)	Seldom n (%)	Never n (%)	N/A n (%)
Do you use TH after adult cardiac arrest?	48	2 (4)	11 (23)	6 (13)	5 (10)	24 (50)
Do you use TH after paediatric cardiac arrest?	46 ^a	0	2 (4)	14 (30)	30 (65)	0

TH: therapeutic hypothermia, ^a percent total greater or less than 100 due to rounding.

4.5.8 Knowledge of the use of therapeutic hypothermia

90% (43/48) of emergency medicine consultants were aware of the literature regarding the use of TH in adults post cardiac arrest.

Very few used TH after paediatric cardiac arrest; 65% (30/46) reported use as 'never' and 30% (14/46) 'seldom'. No responder had a paediatric specific TH protocol in their Emergency Department.

A larger proportion used TH after adult cardiac arrest; 27% (13/48) reported 'always' or 'often'. However, half answered 'not applicable' as they did not manage post-cardiac arrest adults. 17% (8/46) reported being aware of an adult TH protocol in their Emergency Department.

The majority (89%; 42/47) did not know if TH improved outcome after paediatric cardiac arrest.

4.5.9 Patient selection

A number of variables were involved when deciding which patients should receive TH. There were also a number of reasons reported by clinicians for not using TH after cardiac arrest (table two). 52% (25/48) responded to the 'reasons stated for selecting patients for TH' and 88% (42/48) responded to the 'reason stated for not using TH post cardiac arrest'. The most frequent reason for selecting patients was 'on advice from the regional PICU'. Similarly, 24% (10/42) would not use TH as it was not advocated by the regional PICU and 14% (6/42) would transfer patients quickly to PICU and felt therapy could be commenced there with minimal delay rather than in the Emergency Department. The likelihood of patient recovery was also important for 32% (8/25) who used TH in choosing which patients should receive it.

Table 4-6 Selection of patients for therapeutic hypothermia (survey two)

	n (%)
Factors stated in selecting patients for TH post paediatric cardiac arrest (n = 25)	
On advice from PICU	17 (68)
Likelihood of patient recovery after the arrest	8 (32)
Absence of life limiting condition	6 (24)
Availability of equipment	6 (24)
Reasons stated for not using TH post paediatric cardiac arrest (n = 42)	
No equipment available	11 (26)
Not enough research evidence	10 (24)
Not advocated by regional PICU	10 (24)
Not in the Advanced Paediatric Life Support guidelines	9 (21)
Rapid transfer to PICU where TH is usually started	6 (14)
Technically too difficult	6 (14)
Not considered for children	3 (7)
Not an Emergency Department priority or too infrequent	3 (7)
The cooling method available is too slow	2 (5)

4.5.10 Methods of inducing hypothermia

Availability of equipment was reported as a factor in patient selection for TH, and conversely, lack of equipment was reported as a reason for not using TH (Table 4-6).

A wide variety of equipment was available in Emergency Departments (Table 4-7). Equipment was considered available if *any* Consultant from an Emergency Department reported it available. Notably, there were discrepancies between responses from within the same Emergency Department regarding available equipment (mean inter-responder agreement score within each Emergency Department was 0.37; standard deviation 0.06). 86% (18/21) of Emergency Departments had access to wet linen and 81% (17/21) to ice packs. Cold air circulating blankets were reported to be present in 62% (13/21) of Emergency Departments although only 36% (15/42) of individuals reported it being available. There was a median of three methods of cooling (range 1-6) at each Emergency Department.

Table 4-7 Availability of methods for inducing therapeutic hypothermia reported by individuals and per Emergency Departments (survey two)

Methods	Consultant (n=42) Response n (%)*	Emergency Department availability (n=21) n (%)*
Wet linen	35 (83)	18 (86)
Ice-pack to skin	24 (57)	17 (81)
Cold air blanket	15 (36)	13 (62)
Iced cold (4°C) intravenous saline	9 (21)	5 (24)

4.5.11 Opinions regarding future research into therapeutic hypothermia after paediatric cardiac arrest.

A position of clinical equipoise is defined as the existence of an honest, professional disagreement among expert clinicians about the preferred treatment (Freedman, 1987). 52% of emergency medicine consultants agreed or strongly agreed that this exists regarding the use of TH after paediatric cardiac arrest. Only 7% 'disagreed' and the remainder were neutral (Table 4-8).

91% would agree to their patients being recruited into a RCT of TH after paediatric cardiac arrest. There was greater support for a trial of TH versus normothermia than there was for a method of cooling trial. There was strong support that a RCT of TH is ethical (87%), and that deferred consent is appropriate (74%).

Table 4-8 Opinions regarding therapeutic hypothermia randomised controlled trial (survey two)

Statement:	n	Agreement † (%)	n	Mean ‡	SD*
I currently feel there is clinical equipoise regarding the use of hypothermia versus normothermia after cardiac arrest in children	46	24 (52)		3.5	0.69
It is ethical to perform a randomised controlled trial of hypothermia therapy in children after cardiac arrest	46	40 (87)		4.2	0.72
It is ethical to use deferred consent in clinical trials investigating therapies immediately after cardiac arrest	46	34 (74)		3.8	1.10
Would you:	n	Yes n (%)	No n (%)	Don't Know n (%)	
Support a comparative intervention trial?	47	40 (85)	2 (4)	5 (11)	
Support a method of cooling study?	45	34 (76)	5 (11)	6 (13)	
Allow your patients to be recruited to an RCT?	47 ^a	43 (91)	1 (2)	3 (6)	
Use a trial protocol in your ED?	48	41 (85)	1 (2)	6 (13)	

† Agreement = percentage responding 'agree' or 'strongly agree'

‡ Mean score on a Likert scale: 5 (strongly agree), 4 (agree), 3 (neutral), 2 (disagree) and 1 (strongly disagree)

*SD = standard deviation

^a percent total greater or less than 100 due to rounding.

4.6 DISCUSSION

These two surveys suggests that very few UK Emergency Medicine consultants currently initiate therapeutic hypothermia (TH) after paediatric cardiac arrest in their Emergency Departments and there is wide variation in the use of TH after cardiac arrest in children in PICUs in the UK.

4.6.1 Use of therapeutic hypothermia

Approximately 50% of PIC consultants report 'always' or 'often' using it, despite an absence of published, paediatric specific, literature to support its use. However, the vast majority of emergency medicine and PIC consultants in these surveys do not know if TH improved neurological outcome after paediatric cardiac arrest. There is awareness amongst the emergency medicine consultants of adult post-ventricular fibrillation cardiac arrest TH studies which have demonstrated a reduction in bad neurological outcome when treated with TH rather than normothermia (Bernard et al, 2002; Arrich et al, 2009; HACA, 2002).

The 2006 International Liaison Committee on Resuscitation guideline recommended the consideration of hypothermia therapy after paediatric cardiac arrest (ILCOR, 2006). A more recent edition of the ILCOR guideline has been published since these surveys were carried out (Kleinman et al, 2010). However, the recommendations have changed only for adolescents, suggesting that TH is beneficial after ventricular fibrillation cardiac arrest in this group. There has been no paediatric specific RCT. Only two retrospective observational cohort studies (Fink et al, 2010; Doherty et al, 2009) have been published in this area, but they use unbalanced groups and show no difference in outcomes of patients receiving TH compared with normothermia. This lack of evidence may therefore explain the demonstrated lack of uptake of this recommendation. The ongoing Therapeutic Hypothermia After Paediatric Cardiac Arrest (THAPCA) multi-centre RCT (NCT00878644; NCT00880087) in North America and Canada may gather important data on safety and efficacy to strengthen any future guidance.

The role of the regional paediatric intensive care team appears to strongly influence the management of paediatric post cardiac arrest patients in the Emergency Department. Of emergency medicine consultants who would consider using the therapy, 68% reported that they would only commence it if their regional PICU requested and advocated it. Also, if the time taken to admit to PICU was anticipated to be short then therapy would be delayed until that point.

4.6.2 Methods for inducing therapeutic hypothermia

A number of methods of cooling appear to be accessible in most Emergency Departments. However, between consultants from the same Emergency Department, there is discrepancy in the perception of what equipment is available. There was a belief that the PICU would have access to more sophisticated cooling equipment and be able to administer the therapy more safely. This may be due to lack of personal experience and infrequent use of the equipment. The regional variation of paediatric intensive care practice and the low proportion of PIC consultants who would consider starting the therapy in the Emergency Department support the findings from survey two.

Simple surface methods of cooling were used by all PIC consultant responders, with the majority reporting using more than one method. Of interest is the small number (5%) who reported to use 4°C iced intravenous saline to induce therapeutic hypothermia, a method demonstrated to be both safe and effective in adults and children in inducing therapeutic hypothermia (Bernard et al, 2003; Kim et al, 2005; Kim et al, 2007; Fink et al, 2010).

4.6.3 ‘Dose’ of hypothermia

The ‘dose’ of hypothermia appears to be an important element in the potential efficacy of therapeutic hypothermia. The wide variation reported by PIC consultants in duration and depth of cooling and also rate of rewarming reflects the lack of clear evidence. Very few centres reported following a unit protocol which would assist in unifying centre practice. Uncertainty may also be present after the reporting of a trend towards increased harm in an RCT using therapeutic hypothermia after paediatric traumatic brain injury (Hutchison et al, 2008).

85% (55/65) of PIC consultants stated they select duration of cooling between 24 to 48 hours although durations outside this range are also considered. The two adult therapeutic hypothermia RCTs used 12 or 24 hours duration (Bernard et al, 2002; HACA, 2002) whilst the neonatal studies of hypoxic ischaemic encephalopathy have used 72 hours duration (Gluckman et al, 2005; Shankaran et al, 2005; Eicher et al, 2005; Azzopardi et al, 2009). Survey one demonstrates a stated duration of treatment falling between the two sets of published data. Without specific safety data in children the potential risks of longer duration of cooling are not known.

4.6.4 Clinical equipoise, trial support and deferred consent

73% (82/113) of PIC consultants and 52% (24/46) of emergency medicine consultants agreed that there is clinical equipoise regarding the use of TH after paediatric cardiac arrest, although another 41% (19/46) of emergency medicine consultants were 'neutral'. The presence of clinical equipoise remains a fundamental pre-requisite to undertaking a randomised controlled trial (Freedman, 1987). There is strong support among emergency medicine consultants (85%; 40/47), although less (47%; 53/113) amongst PIC consultants for a comparative trial of TH versus normothermia in paediatric patients post cardiac arrest.

The recently commenced Therapeutic Hypothermia After Paediatric Cardiac Arrest (THAPCA) trials (NCT00878644; NCT00880087) in North America and Canada will hopefully start to answer the question of safety and efficacy of this treatment in children. There is agreement (83%; 92/112) that the results of these trials are likely to inform clinical practice in the UK, but the support for a study also to be undertaken in the UK perhaps reflects that a number of trials showing an effect are required to change clinician's behaviour.

The use of deferred consent is a new area in paediatric resuscitation research in the UK. Recent changes in April 2008 to the Medicines for Human Use (Clinical Trials) Regulations, UK 2004 have allowed the use of deferred consent (with Ethics Committee approval) to be applied to emergency resuscitation research (Department of Health, 2008). In these surveys

88% (99/113) of PIC and 74% (34/46) emergency medicine consultants supported the use of deferred consent. The use of deferred consent in a clinical trial may enable earlier instigation of therapy within the narrow therapeutic window and therefore maximise the potential beneficial effects.

4.6.5 Strengths and limitations of surveys

One of the strengths of these surveys is the high response rates of 76% (113/149) and 62% (48/77). A targeted approach, in survey one, to a defined population of UK PIC consultants with direct clinical involvement and decision making regarding patient care enable a degree of confidence that these findings reflect the current UK PIC community practice. However, not all UK emergency medicine consultants were surveyed in survey two, potentially missing some of those who manage paediatric cardiac arrest patients. As with all surveys however, the findings only represent self-reported behaviour and do not necessarily equate to actual clinical behaviour. The findings give additional support for the need and willingness to undertake further investigative research into the use of therapeutic hypothermia after paediatric cardiac arrest.

4.7 CONCLUSION

These surveys of practice and opinions found that very few UK emergency medicine consultants initiate therapeutic hypothermia in their Emergency Departments and only 50% of paediatric intensive care consultants currently use TH use after paediatric cardiac arrest. Regional paediatric intensive care units and consultants play significant roles in influencing the management of paediatric cardiac arrest patients in the Emergency Department. With their support, Emergency Department consultants would consider using therapeutic hypothermia. Although simple methods of cooling patients are already available in most Emergency Departments, their use is limited owing to clinician concerns regarding safety, lack of protocols, and lack of evidence of improved outcomes.

There is support among UK paediatric intensive care and emergency medicine consultants for further research into the safety and efficacy of therapeutic hypothermia. This research would require involvement of emergency medicine consultants and their departments in order to be able to initiate therapeutic hypothermia early. These surveys support the proposal that the feasibility of the Cold-PACK (Post Arrest Cooling In Kids) Study of therapeutic hypothermia versus normothermia commenced in the Emergency Department after paediatric cardiac arrest should be assessed further.

Table 4-9 Chapter 4 and RCT feasibility

What have we learnt from this study towards the feasibility of a UK randomised controlled trial?

In the UK approximately half of paediatric intensive care consultants use therapeutic hypothermia after paediatric cardiac arrest

It is infrequently used in the emergency department and only after advice from a paediatric intensivist

There is widespread variation in the dose and duration of therapeutic hypothermia used

Clinical equipoise exists and there is currently support for a UK multicentre trial

4.8 ACKNOWLEDGEMENT

We are indebted to the paediatric intensive care and emergency medicine consultants in the UK who took the time to complete this survey and we thank Mr David Scholefield for the web-based support and survey design.

4.9 CONTRIBUTORSHIP

4.9.1 Survey one

Dr Scholefield designed the data collection tools, monitored data collection, analysed the data, and drafted the published manuscript. Drs Duncan and Morris piloted the data collection tool, analysed the data and revised the paper.

4.9.2 Survey two

Drs Scholefield and Dr Lyttle designed data collection tools, monitored data collection and analysed the data. Dr Scholefield drafted, revised the manuscript and is guarantor. Dr Lyttle revised the published manuscript. Drs Berry, Duncan and Morris piloted data collection tool, analysed the data and revised the paper. Mr David Scholefield adapted the data collection tool for internet use for both surveys.

5 Cardiac arrest requiring intensive care admission: A United Kingdom epidemiology study.

*"The essence of knowledge is, having it, to apply it;
not having it, to confess your ignorance."*

Confucius (Chinese teacher and social philosopher: 551–479 BC)

Part of this chapter has been presented at conference:

Scholefield B, Duncan, H, McShane, P, Parslow R, Tasker R, Gao F, Morris, K.
Cardiac arrest requiring intensive care admission: A UK epidemiological study.
Presented at the 6th World Paediatric Critical Care Conference Sydney, March 2011
(Abstract). *Pediatr Crit Care Med*, 2011, Vol 12 No 3 (page A6)

5.1 ABSTRACT

5.1.1 Introduction

The incidence rate of paediatric cardiac arrest admissions to PICU in the UK is not known and extrapolation of international data to the UK population may not be appropriate when planning a UK post cardiac arrest intervention trial. Different patient characteristics and outcome after in-hospital cardiac arrest (IHCA) and out-of-hospital cardiac arrest (OHCA) may also preclude combining the populations in a unified trial. An understanding of the UK paediatric cardiac arrest population admitted to PICU is therefore essential.

5.1.2 Aims

To compare the epidemiology of children (0-18yrs) admitted to UK paediatric intensive care units (PICUs) after IHCA and OHCA in order to evaluate PICU admission characteristics and patient populations critical to the design of a post cardiac arrest intervention trial.

5.1.3 Methods

Extraction and analysis of IHCA and OHCA admissions from the prospectively collected national PICANet Database containing information on admissions to 30 PICUs in the UK and Eire between January 2003 and June 2010.

5.1.4 Results

1703 children were admitted to PICU following cardiac arrest (51% IHCA, 49% OHCA). Median age of IHCA was significantly lower (0.6 (IQR [0.2-3.0] vs. 1.1 (IQR [0.2-7.8]) years). Pre-existing chronic conditions were more common in IHCA (79%) than OHCA patients (48%). 74% of OHCA were admitted from other hospitals requiring inter-hospital transportation to PICU compared to 41% of IHCA. Pupils were fixed and dilated in 24% of OHCA versus only 5% of IHCA admissions ($p<0.001$) and associated with a 96% and 84% PICU mortality respectively. PICU survival was significantly higher for IHCA patients (76% versus 50%; $p<0.01$). OHCA admission to PICU population incidence rate was 1.3 per 100,000 children (0 to 15 years) per year (patients <1 year of age incidence rate = 8.9). IHCA and OHCA each accounted for 0.8% (IQR [0.6–1.0]) of all PICU admissions. A UK

interventional trial of IHCA would require 482 patients and take 3.7 years, and an OHCA would require 776 patients and take 6.9 years if powered to show a 10% absolute improvement in survival (IHCA [76% to 86%] and OHCA [50% to 60%]).

5.1.5 Conclusions

Survival rates to PICU discharge after IHCA and OHCA appear higher than previously reported. Differences between IHCA and OHCA population demographics, aetiology of arrest and survival rates would preclude combining both groups in a single cardiac arrest study. The UK population incidence rates suggest that international collaboration will be required for a post cardiac arrest intervention trial to be delivered in a reasonable timescale.

5.2 INTRODUCTION

A fundamental requirement before undertaking research in children after cardiac arrest is to fully understand the population. The answers to three important questions are essential. First, how large is the potential population affected by cardiac arrest in the UK and therefore available for inclusion in a trial, secondly, can we combine patients after both in-hospital cardiac arrest (IHCA) and out-of-hospital cardiac arrest (OHCA) in the same trial, and thirdly what are the current outcome rates after cardiac arrest in contemporary UK practice? Without answering these questions an interventional trial risks failing to recruit enough patients, being underpowered to detect a treatment effect or including a heterogeneous population where the treatment effect differs significantly across subjects, culminating in a waste of resources (time and money) and importantly exposing critically ill children to unnecessary risks in a trial which fails to answer its primary objective.

There are currently no UK paediatric cardiac arrest incidence or outcome data available to answer these questions. Extrapolating OHCA incidence rates from other national population studies may be inappropriate. Published incidence rates of OHCA alone range from 5 to 20 per 100,000 person-years across different populations with rates of return of spontaneous circulation (ROSC) ranging from 5-47% (Donoghue et al, 2005; Deasy et al, 2010; Dieckmann & Vardis, 1995; Lopez-Herce et al, 2005; Nitta et al, 2011). Using these wide ranges, the number of patients in the UK admitted to PICU after OHCA would be estimated at between 50 and 1000 children per year and therefore completely unhelpful for confidently planning a clinical trial.

It is anticipated that the number of patients in the UK surviving to PICU admission after IHCA and OHCA will be relatively small. Combining the two populations would therefore be an attractive option; however, if this creates a heterogeneous population further problems are created. Critical care randomised controlled trials in adults have repeatedly failed to deliver evidence of beneficial treatments owing to use of heterogeneous populations, lack of biological plausibility, over estimating potential treatment effects based on observational study evidence and importantly under-powering of studies through failing to recruit to target (McAuley et al, 2010). Therefore, the assessment of the differences between IHCA and

OHCA including the survival rates is a high priority to avoid creating too great a heterogeneous population. In addition, an accurate estimation of the patient population to assess trial feasibility, prior to costly investment, is required.

This study therefore aims to answer the three fundamental questions outlined above using data collected through the Paediatric Intensive Care Audit Network (PICANet). This is a national data collection programme of all Paediatric Intensive Care Unit (PICU) admissions in the UK and Eire. Analysis of the cardiac arrest population in this database will allow an assessment of incidence, patient population size, key patient characteristics and outcome to hopefully inform future trial development.

5.3 AIMS

5.3.1 Primary Aim

1. To identify a population of children (0 to 17yrs) admitted to UK paediatric intensive care units (PICUs) after in-hospital (IHCA) and out-of-hospital cardiac arrest (OHCA).

5.3.2 Secondary Aim

1. To ascertain PICU survival rates and associated factors after IHCA and OHCA.
2. Calculate the incidence of IHCA and OHCA admissions to PICU in the UK.
3. Estimate the size of the cardiac arrest population available for inclusion in a post cardiac arrest intervention trial.

5.4 METHODOLOGY

5.4.1 Design

A standardised dataset consisting of casemix and PICU outcomes of all patients admitted to all 30 PICUs from the United Kingdom and Eire has been prospectively collected since 2002 by the Paediatric Intensive Care Audit Network (PICANet, 2010). Training on data definition and data collection has been performed by the PICANet team with local and central quality, validation, illogicality and completeness checks on data (PICANet, 2010).

5.4.2 Settings and participants

In October 2010, we retrospectively searched the PICANet database from Jan 2003-June 2010 for all patients admitted to PICU after cardiac arrest. Inclusion and exclusion criteria are listed below.

Inclusion criteria

1. Aged 0 to 17 years and
2. Admitted to PICU after either IHCA or OHCA and
3. Patients requiring intubation and ventilation on admission

Exclusion criteria

1. Cardiac arrest occurring after admission to PICU

Cardiac arrest was defined *a priori* by PICANet as either documented absent pulse or the requirement for external cardiac compression (PICANet, 2007). This PICANet definition did not specify a length of CPR, therefore, to exclude very minor, short cardiac arrests (e.g. brief episode of bradycardia) and patients likely to still be comatose, the additional requirement of intubation and ventilation at time of PICU was added. Accurate data on cardiac arrest occurring on PICU were only recorded through the Paediatric Critical Care Minimum Data Set (PCCMDS) (an addition to the main PICANet dataset) which commenced in June 2008. Owing to a low number of PICUs submitting PCCMDS data it was not possible to ascertain accurate in-PICU cardiac arrest events; therefore this group was excluded from analysis.

Readmissions to PICU were analysed as separate admissions because each admission represented a separate opportunity for a PICU outcome.

5.4.3 Data collection and search criteria

Search criteria and codes to identify eligible patients are listed in Table 5-1. The PICANet data collection form had a place to record either IHCA or OHCA as a *high risk diagnosis* in the patient's medical history when clinicians scored the Paediatric Index of Mortality 2 score (PIM2 score) on admission to PICU (PICANet, 2006; Slater et al, 2003). An OHCA was referred to as 'preceding hospital CPR' in the PICANet coding and an IHCA as 'preceding CPR'. A group of patients after June 2008 had additional PCCMDS data collected daily during their PICU admission, indicating if CPR occurred on day one of admission or after day one implying that the cardiac arrest occurred whilst on the PICU. In addition, at discharge, all patients had final diagnostic codes entered into the database. This allowed entry of a text descriptions of cardiac arrest diagnosis combined with NHS Read Codes (a coded thesaurus of clinical terms) (Bentley et al, 1996). Examples of text diagnosis include: 'arrested whilst drowning' indicating an OHCA, 'arrested in theatre' indicating an IHCA and 'arrested during intubation on PICU' indicating an in-PICU arrest (IPICA). Ideally, all patients would be reliably allocated to IHCA and OHCA using only the admission PIM2 coding. However, in some PICUs both 'preceding hospital CPR' and 'preceding CPR' were selected for OHCA patients and frequently, the coding of IHCA and OHCA arrest location in PIM2 was missing in the dataset. Therefore, owing to the inconsistent primary coding of location of arrest, an allocation matrix was created using a combination of all the coding criteria in the PICANet dataset referring to cardiac arrest in order to code patients into four categories; 1) IHCA, 2) OHCA 3) In PICU (after PIC admission) arrest and 4) other (unclassifiable). The *Allocation Matrix* is displayed in Table 5-2. The matrix consisted of a combination of the PIM2 codes from admission, additional PCCMDS codes during admission and final diagnostic text codes. Thereby including: preceding hospital CPR, preceding CPR, CPR on day one of PICU admission, CPR after day one of PIC admission, text diagnosis with OHCA description, IHCA description, and IPICA and source of admission (e.g. emergency

department for OHCA but not IHCA). Patients with incomplete information, where location of arrest could not be ascertained were categorised 'other' and therefore excluded.

5.4.4 Casemix, resource use and outcome

In addition to the variable used to allocate cardiac arrest location, additional casemix variables collected were; admitting PICU, year of admission, age, sex, source of admission (e.g. ward or emergency department), primary and secondary diagnoses, probability of death (estimated from PIM 2 score) and transfer status to PICU (e.g. admitted from own hospital emergency department or secondary hospital). PIM2 is a prediction of mortality score calculated within one hour of contact with the paediatric intensive care team (either on PICU or a specialist critical care transport) (Slater et al, 2003). Age was subdivided using two grouping classifications. Firstly, Utstein derived age strata (0 to 30 days, 31 days up to 1 year, 1 year up to 4 years, 4 years up to 12 years and 12 years up to 18 years) (Zaritsky et al, 1995) for comparison with other published cardiac arrest databases and Office of National Statistics (ONS, 2010) age strata (1 day up to 1 year, 1 year up to 4 years, 4 years up to 10 years, 10 years up to 15 years and 15 years up to 18 years) for incidence rate calculations.

Table 5-1 Search codes for cardiac arrest patients

Domain	Cardiac arrest description	
PIM2 medical history	Preceding hospital cardiac arrest	
PIM2 medical history	Preceding CPR episode	
Text diagnostic codes	Cardiac arrest, cardiopulmonary arrest, cardiorespiratory arrest & ventricular fibrillation (or VF), ventricular tachycardia (or VT), asystole, pulseless electrical activity (or PEA)	
NHS Read codes	G5740	Cardiac arrest - ventricular fibrillation
	L09y1	Cardiac arrest following abortive pregnancy
	SP110	Cardiac arrest as a complication of care
	X202m	Cardiopulmonary arrest
	X202n	Cardiac arrest with successful resuscitation
	X208V	Cardiac arrest with electromechanical dissociation
	X77CB	Cardiac arrest - asystole
	X90DE	Circulatory arrest
	XE0V5	Cardiac arrest
	XaC2L	Cardiac arrest, unspecified
	Xa08p	Infant showing no response to resuscitation
	Xa8S8	CPR - Cardiopulmonary resuscitation

PIM2 denotes: paediatric index of mortality 2 score

Table 5-2 Allocation matrix

Preceding Hospital CPR	Preceding CPR	Day 1 CPR on PCCMDS	Day >1 CPR on PCCMDS	Text diagnosis with OHCA code	Text diagnosis with IHCA code	Text diagnosis with IPICA code	ED Source of admission	GROUP	
+	+/-	+/-						OHCA	included
-	-	+/-		+				OHCA	
-	+	+						IHCA	
-	+	-					-	IHCA	
-	+	n/a	n/a	-		-		IHCA	
-	-	+/-		-	+	-		IHCA	
-	-	+	+					IPICA	Excluded
-	-					+		IPICA	
-	+	-	+	-	-	-	+	Other	
-	+	n/a	n/a	-	-	-	+	Other	
-	-	-	-	-	-	-	+/-	Other	

Plus sign = present, minus sign = absent, n/a = not applicable

CPR: cardiopulmonary resuscitation, PCCMDS (paediatric critical care minimum dataset), IPICA: in-PICU arrest, ED: emergency department

Data on resources used on PICU were collected which included renal replacement therapy (including haemofiltration, haemodialysis and peritoneal dialysis), vasoactive drug use, intracranial pressure monitoring and extracorporeal life support (ECLS). Primary outcome was survival to PICU discharge. Survival data after this point (e.g. hospital survival) was not accurately collected in the PICANet dataset. Length of ventilation and stay on PICU was recorded. These were both calculated in days, where ventilation or stay on PICU for any part of the period from midnight to midnight counted as one day (PICANet definition) (PICANet, 2007).

5.4.5 Chronic condition coding

Chronic condition diagnostic groups were decided *a priori*: respiratory, neurological, cardiac, liver, haematology, oncology, metabolic and endocrine, gastrointestinal, renal, genetic, immunodeficiency and other. All diagnostic text codes contained in the database were listed and duplicates removed. Each diagnostic code and free text diagnostic description was allocated to a chronic condition group and subgroup (Appendix 9.9, p330). Individual patients could be allocated into multiple coding groups (e.g. neurological, genetic and cardiac condition).

5.4.6 Cause of arrest coding

A separate coding system was used for cause of arrest. Admissions were allocated to only one cause of arrest: respiratory, sepsis, neurological (non-trauma), primary cardiac, trauma, airway obstruction, hanging (or strangulation), burns, toxin ingestion, near-drowning or unknown or not clearly defined. This was performed by individually allocating each patient based on final discharge diagnosis information. If the diagnosis may have referred to an event after PIC admission then cause of arrest was recorded as 'not known'.

5.4.7 Denominator population

Individual PICU admission numbers were extracted from the main PICANet dataset to calculate unit-specific admission rates for IHCA and OHCA patients. Age specific population counts were extracted from the mid-2008 population estimates for Great Britain (Office of

National Statistics) (ONS, 2010). This allowed calculation of age-specific incidence rates for OHCA admission to PICU. It was not possible to calculate IHCA admission to PICU incidence rates. Ideally total in-patient numbers per year for all hospitals referring to each individual PICU would be required. However, owing to cross over of secondary hospital to PICU referrals (i.e. patients from a secondary hospital could be sent to more than one PICU) and significant inconsistencies in the data in the Hospital Episode Statistics database (HES, 2012), this was not calculated.

5.4.8 Population size calculations

To estimate the population size available for inclusion into a randomised controlled post cardiac arrest intervention trial, individual PICU-specific patient numbers were extracted for IHCA and OHCA admissions between 2007 and 2009. We anticipate the need for additional exclusion criteria in a randomised control trial. Therefore, the following patients were excluded from the dataset for sample size estimation: patients admitted after traumatic brain injury, patients with severe developmental delay (coded on PIM2 high risk medical history), patients aged 16 years and older and finally, those dying within six hours of PICU admission.

Patients with traumatic brain injury were excluded because of the current evidence of therapeutic hypothermia causing harm in the population (Hutchison et al, 2008). Patients with severe developmental delay may already have limitation of intensive care support plans on admission and have very poor baseline level of neurological function, and patients aged 16 and over are often admitted into adult ICUs, although regional variation across the UK exists. Excluding patients dying within six hours will exclude patients at the very severe end of the spectrum who would be very unlikely to benefit from post cardiac therapeutic hypothermia therapy.

5.4.9 Statistical analysis

Data were tested for normality by using the Shapiro-Wilk's W test. Descriptive data were reported as median and interquartile range (IQR) or mean \pm standard deviation (95% confidence interval of the mean) for continuous variables and as number and percentages for categorical variables. Casemix, cause of arrest, resource use and outcomes were

compared between IHCA and OHCA patient groups. Parametric continuous data were analysed using the unpaired Student t-test and non-parametric continuous data with the Mann Whitney U test or Kruskal-Wallis as appropriate. Length of ventilation and length of stay were log-transformed prior to analysis. Categorical data were analysed using the Chi² or Fisher's exact tests as appropriate. Linear by linear association (SPSS) was used for age related ordinal categorical data.

A multivariate logistic regression analysis was used to identify variables that were independently associated with survival. Normality and linearity of continuous variables was assessed. Initially, associations with outcome were identified by univariate logistic regression analysis. Then all variables with $p < 0.1$ for survival were included in a multivariate logistic regression analysis model. Forward stepwise selection was applied to this group of potential predictors to obtain the final model. The criteria for variable selection were a significance level (p value based on likelihood ratio test) to enter of 0.05 and a significance level to stay of 0.10. Hosmer Lemeshow goodness of fit and area under the receiver operator characteristic (ROC) curve were calculated to assess model fit (Hanley & McNeil, 1982; Hosmer et al, 1997).

5.4.10 Statistical analysis: sample size calculation

Incidence rate of OHCA admission to PICU was calculated using Wilcoxon Signed Rank test to calculate the median (95% confidence interval (CI)) rate on data from a subset of patients admitted between 2007 and 2009. Denominator data was extracted from the Office of National Statistics mid-2008 population estimates (as detailed above) (ONS, 2010).

Future trial sample size calculations were performed on unadjusted mortality rates and individual PICU patient population admission rates. They were estimated over a range of treatment effects (7% - 20%) with increasing numbers of PICUs, using two-sided significance (α) level of 0.05 and power ($1-\beta$) of 80%.

A two sided p value of <0.05 was considered statistically significant throughout. Data analysis was performed using either IBM-SPSS Statistics version 19.0 software (SPSS Inc, Chicago, USA) or Minitab 16 (USA).

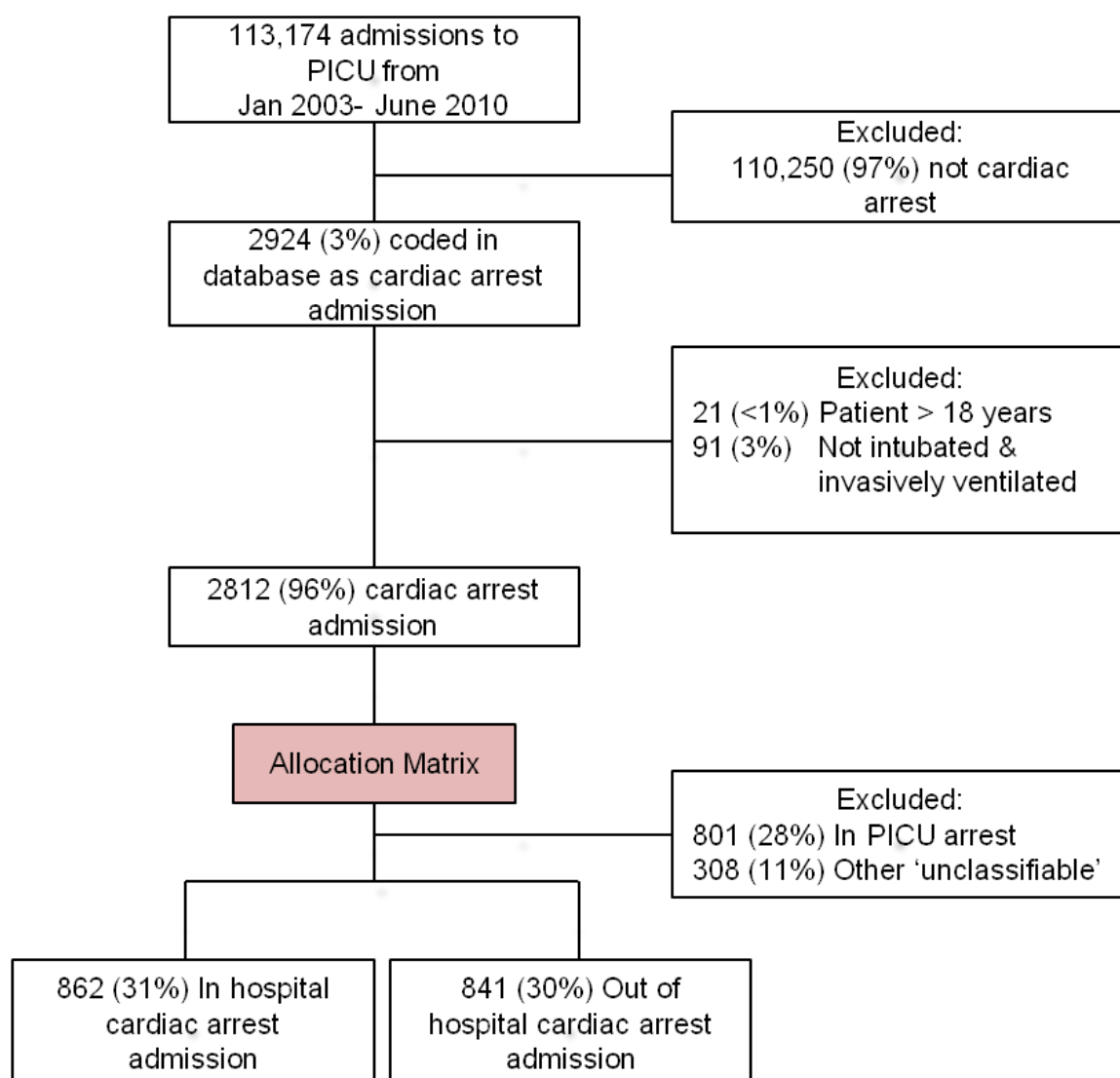
5.4.11 Ethics

PICANet has ethical approval granted by the Trent Medical Research Ethics Committee (ref 05/MRE04/17) and national information governance board approval by the Patient Information Advisory Group <http://www.dh.gov.uk/ab/index.htm> to collect personally identifiable data without consent. The original search for this study (described above) of the main PICANet dataset was performed by Dr Phil McShane (PICANet Senior Epidemiologist). Patient identifiable data and the name of admitting PICU were then anonymized before encrypted transfer to the author for analysis.

5.5 RESULTS

Figure 5-1 shows the study plan. 2924 patients were identified as cardiac arrest cases. After exclusion of cases older than 18 years ($n=21$) or not intubated and ventilated on PIC admission ($n=91$), 2812 remained. These patients were allocated to their source of arrest groups using the *Allocation Matrix* (Table 5-2). 64% (1812/2812) were coded directly as IHCA or OHCA preceding PIC admission in the PIM2 dataset, the remaining 36% required allocation through text diagnosis or CPR event history. This resulted in 862 IHCA cases, representing 0.8% (IQR [0.6 – 1.0%]) of total PICU admissions and 841 OHCA cases, 0.8% (IQR [0.7% - 1.0%]) of total PICU admissions during this period. A further 801 only had a cardiac arrest whilst on the PICU and were excluded in addition to 308 patients who could not be categorised.

Figure 5-1 Study flow chart



5.5.1 Demographics

Age of patients admitted after IHCA and OHCA are presented within Utstein and ONS age limits (Table 5-3). IHCA patients were significantly younger than OHCA ($p<0.01$). A significant left skew to age was identified for both groups (Figure 5-2). 58% and 49% of patients were less than 1 year of age for IHCA and OHCA respectively. An increase in proportion of OHCA patients aged 10-15yrs was identified. There was no difference in survival with increasing age for OHCA ($p=0.582$); however IHCA survival showed a statically significant survival increase across Utstein ($p=0.05$) and ONS ($p<0.001$) age groups (Figure 5-4).

Chronic conditions were more common in IHCA patients (79% versus 48%; $p<0.001$). Of which cardiac, neurological and respiratory conditions predominated in both groups. After OHCA, patients with no recorded chronic conditions had a higher mortality compared to those with one or more chronic condition (60% vs. 40%; $p<0.001$). Comparison of chronic conditions and corresponding PICU mortality rates are displayed in Table 5-4.

Nearly three quarters (635/841) of patients admitted after OHCA were transported from another hospital for PIC admission compared to 41% (381/862) after IHCA. Overall mortality risk score (calculated using Paediatric Index of mortality 2) on admission was lower after IHCA (25% vs. 38%; $p<0.001$). Fixed and dilated pupils on admission were recorded in 24% (192/841) OHCA and 5% (41/862) IHCA with a very high associated mortality rate (96% and 84% respectively).

Table 5-3 Age casemix for admission comparing IHCA and OHCA

	IHCA	No. died (% group)	OHCA	No. died (% group)	Comparison of IHCA and OHCA <i>p</i> ^b
Overall	n=862	209 (24%)	n=841	423 (50%)	
Age (years; median, IQR)	0.6 (0.2 – 3.0)		1.1 (0.2 – 7.8)		< 0.01
Age category (Utstein ^a)					<0.001
0 -30 days	163 (19%)	44 (27%)	119 (14%)	54 (45%)	
31 days to <1 yr	339 (39%)	64 (19%)	295 (35%)	149 (51%)	
1yr to <4yrs	174 (20%)	43 (25%)	162 (19%)	85 (53%)	
4yrs to <12yrs	107 (12%)	32 (30%)	129 (15%)	69 (54%)	
12yrs to <18yrs	79 (12%)	26 (24%)	136 (15%)	66 (49%)	
Age category (ONS)					<0.001
0 to <1yr	503 (58%)	108 (22%)	415 (49%)	204 (49%)	
1yr to <4yrs	173 (20%)	43 (25%)	161 (19%)	84 (52%)	
4yrs to <10 yrs	86 (10%)	27 (31%)	93 (11%)	47 (51%)	
10yrs to <15 yrs	66 (8%)	16 (24%)	126 (15%)	71 (56%)	
15yrs to <18yrs	34 (4%)	15 (44%)	46 (5%)	17 (37%)	
Male	518 (56%)		505 (58%)		0.678

^a Utstein pre-defined age groups (Zaritsky et al, 1995). Results expressed as Median (Inter-quartile range) or number (percent). ^b Chi² test was used for categorical variable and Mann Whitney U test for continuous variables to compare IHCA and OHCA groups.

Figure 5-2 Comparison of age distribution for IHCA and OHCA patients admitted to PICU

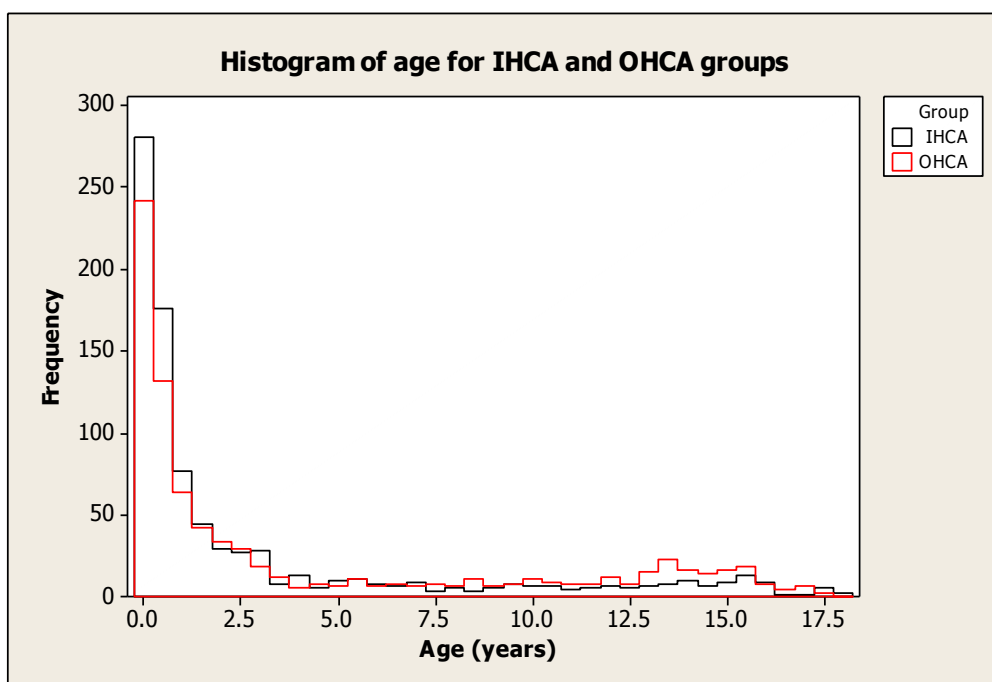


Figure 5-3 Comparison of Utstein defined age groups for IHCA and OHCA patients admitted to PICU

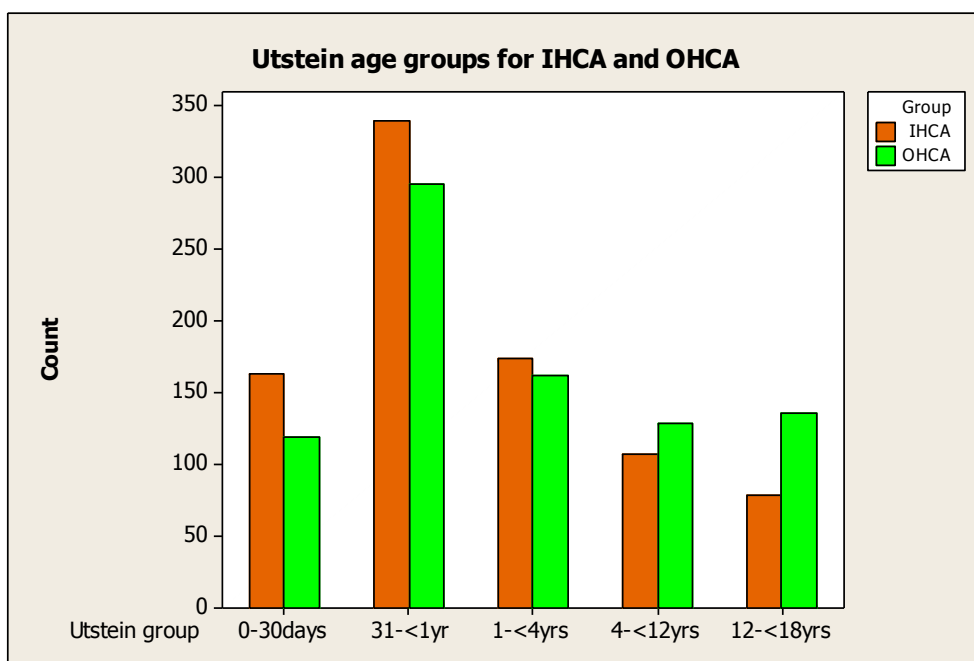


Figure 5-4 Survival comparison for IHCA and OHCA across Utstein age groups

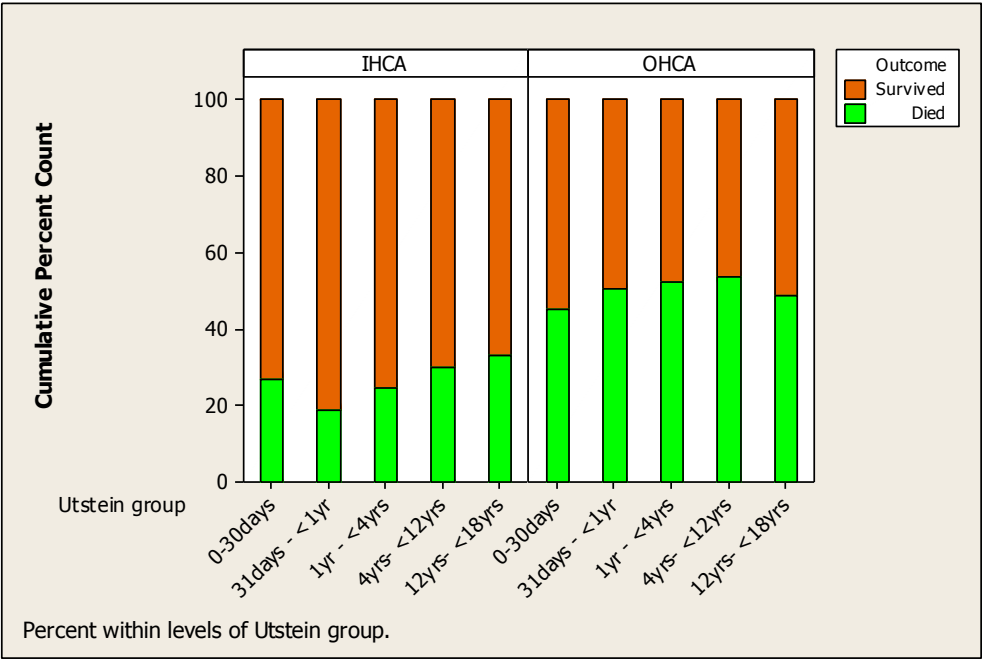


Table 5-4 Chronic condition casemix for admission after IHCA and OHCA

	IHCA N=862	No. died (%condition)	OHCA N=841	No. died (%condition)	<i>P</i> ^a
No Chronic condition	185 (21%)	49 (27%)	440 (52%)	263 (60%)	<0.001
Any chronic condition	677 (79%)	160 (31%)	401 (48%)	160 (40%)	<0.001
Cardiac	318 (37%)	72 (23%)	160 (19%)	48 (30%)	
Neurological	151 (18%)	39 (26%)	122 (14%)	61 (50%)	
Respiratory	213 (25%)	32 (15%)	108 (13%)	28 (26%)	
Prematurity	72 (8%)	11 (15%)	54 (6%)	23 (43%)	
Genetic	70 (8%)	16 (23%)	28 (3%)	14 (50%)	
Metabolic	58 (7%)	19 (33%)	39 (5%)	18 (46%)	
Gastroenterological	51 (6%)	12 (24%)	17 (2%)	6 (35%)	
Renal	30 (4%)	7 (23%)	15 (2%)	5 (33%)	
Oncology	35 (4%)	13 (37%)	6 (1%)	2 (33%)	
Liver	25 (3%)	7 (28%)	7 (1%)	2 (29%)	
Immunological	14 (2%)	3 (21%)	3 (0.4%)	1 (33%)	
Haematological	10 (1%)	6 (60%)	6 (1%)	1 (17%)	
Other	71 (8%)	16 (23%)	55 (7%)	24 (44%)	

Results expressed or number (percent).

^a Chi² test or Fishers exact test was used for categorical variable and Mann Whitney U test for continuous variables to compare IHCA and OHCA groups.

Table 5-5 Additional demographic details on admission IHCA and OHCA

	IHCA N=862	No. died (%group)	OHCA N=841	No. died (%group)	<i>p</i> ^a
Transported from different admitting hospital n (%)	381 (41.4)	103 (28%)	635 (72.9)	321 (52%)	<0.001
Mortality Risk (PIM2) (Med: IQR)	25% (13-46)	n/a	38% (21-73)	n/a	<0.001
Two unresponsive pupils n (%) ^b	41 (5.0%)	36% (84%)	192 (23.6%)	183 (96%)	<0.001

Results expressed or number (percent) or median (interquartile range). ^a Chi² test was used for categorical variable and Mann Whitney U test for continuous variables between IHCA and OHCA groups. ^b Pupil reaction missing in 49 IHCA, 28 OHCA cases

5.5.2 Cause of arrest

Cause of arrest was not known or not ascertainable in 63% (544/862) IHCA cases and 48% (406/841) OHCA cases. Trauma related causes predominated in OHCA group including; hanging or strangulation, near drowning and trauma (including traumatic brain injury and other traumatic injury). Sepsis and respiratory aetiology were more common in IHCA cases. Airway obstruction as a cause of arrest was similar for IHCA and OHCA; however the mortality rates were significantly higher after OHCA (47% vs. 0%; $p = 0.001$)

The relationship between increased mortality in OHCA patients with no chronic conditions is explored in Figure 5-5. Patients with no recorded chronic conditions predominately arrested secondary to high risk aetiologies; burns, hanging and near-drowning.

Amongst the cause of arrest for OHCA, age related trends were observed (Table 5-7). Younger patients were more likely to have an unknown or sepsis cause for cardiac arrest. Hanging or strangulation, toxic ingestion and a presumed cardiac cause predominated in the 12 to 18 year stratum, whilst near-drowning was commonest in the one to four year old age stratum.

Table 5-6 Aetiology of arrest

Cause of arrest	IHCA N=862	No. died (% aetiology)	OHCA N=841	No. died (% aetiology)	<i>p</i> ^a
Not Known	544 (63%)	133 (24%)	406 (48%)	203 (50%)	<0.01
Respiratory	123 (14%)	24 (20%)	100 (12%)	30 (30%)	0.146
Sepsis	108 (13%)	31 (29%)	44 (5%)	25 (57%)	<0.001
Neurological (non-trauma)	28 (3%)	10 (36%)	58 (7%)	46 (79%)	0.001
Cardiac	16 (2%)	1 (6%)	34 (4%)	8 (24%)	0.008
Trauma ^b	21 (2%)	7 (33%)	69 (8%)	46 (67%)	<0.001
Airway obstruction	19 (2%)	0	21 (2%)	9 (47%)	0.809
Hanging or strangulation	0 (0)	0	28 (3%)	19 (68%)	<0.001
Burns	3 (<1%)	0	5 (<1%)	3 (60%)	0.457
Toxin Ingestion	0 (0)	0	15 (2%)	8 (53%)	<0.001
Near-Drowning	0 (0)	0	61 (7%)	28 (46%)	<0.001

Results expressed as number (percent). ^aChi² test or Fishers exact test was used for categorical variables comparing IHCA and OHCA groups. ^bTrauma including traumatic brain injury and other injuries

Figure 5-5 Chart of association between acute aetiology of OHCA and presence of chronic condition

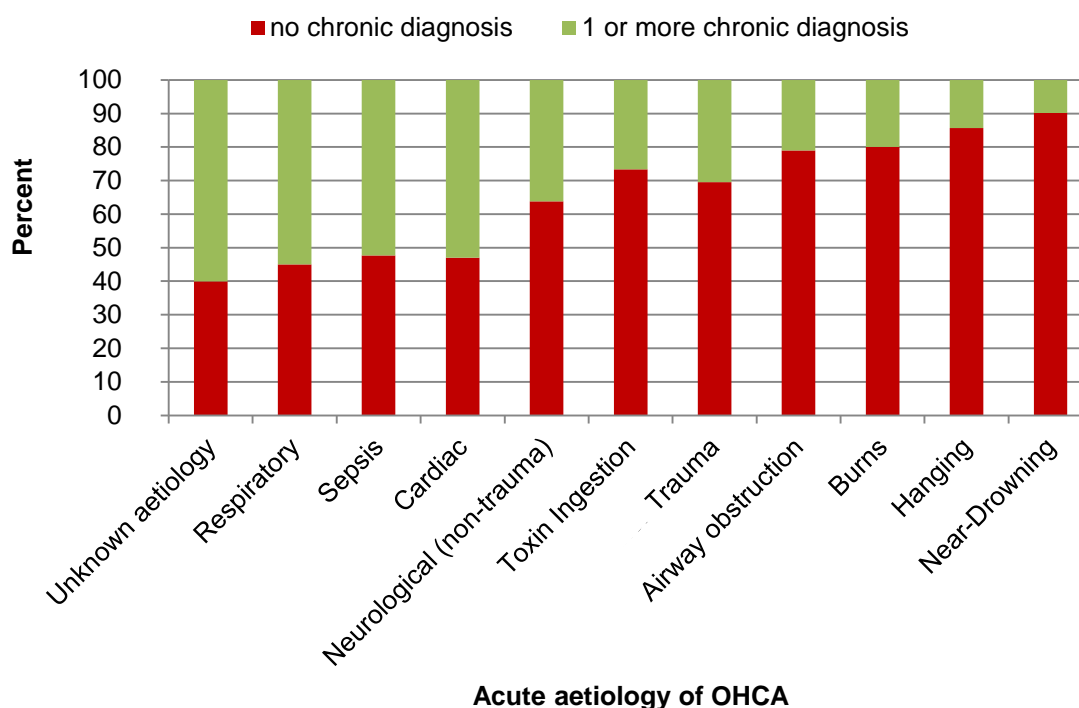


Table 5-7 Aetiology of OHCA by patient age group (Utstein)

Cause of arrest	1-30 days ^a	31 days to <1 yr	1yr to <4yrs	4yrs to <12yrs	12yrs to <18yrs	<i>p</i> ^b
No of patients	n =119	n = 295	n = 162	n = 129	n = 136	
Not Known	74 (62)	176 (60)	55 (34)	62 (48)	41 (30)	<0.001
Respiratory	15 (13)	38 (13)	13 (8)	17(13)	17 (13)	0.915
Sepsis	17 (14)	13 (4)	7 (4)	4 (3)	3 (2)	<0.001
Neurological (non-trauma)	7 (12)	26 (9)	8 (5)	12 (9)	5 (4)	0.352
Cardiac	0 (0)	6 (2)	5 (3)	6 (5)	17 (13)	<0.001
Trauma^c	3 (3)	25 (9)	15 (9)	14 (11)	12 (9)	0.38
Airway obstruction	1 (5)	6 (2)	8 (5)	2 (2)	2 (2)	0.861
Hanging or strangulation	0 (0)	0 (0)	4 (3)	8 (6)	16 (12)	<0.001
Burns	0 (0)	1 (<1)	1 (<1)	2 (2)	1 (<1)	0.192
Toxin Ingestion	0 (0)	1 (<1)	4 (3)	0 (0)	10 (7)	<0.001
Near-Drowning	1 (1)	8 (3)	42 (26)	4 (4)	5 (4)	0.013

^aUtstein pre-defined age groups (Zaritsky et al, 1995). ^bChi² test – linear by linear trend association across age groups. ^cTrauma including traumatic brain injury and other injuries

5.5.3 Interventions on PICU and outcome

Vasoactive drugs were used in 60% of both IHCA and OHCA patients, although renal replacement therapy, intracranial pressure (ICP) monitoring and extracorporeal life support (ECLS) were infrequently performed on post cardiac arrest patients in both groups (only 2-10% of cases) (Table 5-8). There was significantly more renal support performed in the IHCA group (10% vs. 3%; $p<0.001$) whereas ICP monitoring and ECLS use was similar.

The overall length of mechanical ventilation and stay in PICU was significantly shorter after OHCA than IHCA; however, survivors and non-survivors, when compared between IHCA and OHCA groups had similar length of ventilation and PIC stay. The overall difference in length of mechanical ventilation and stay in PIC between IHCA and OHCA is therefore explained by the significantly higher survival after IHCA (76% vs. 50%; $p<0.001$) (Table 5-9).

Multivariable logistic regression analysis showed that the odds of mortality after both IHCA and OHCA significantly increased with increasing PIM2 score, the use of vasoactive drugs and presenting with two fixed and dilated pupils. In addition, odds of mortality after OHCA was increased in patients admitted from a secondary hospital, with a preceding chronic genetic condition or an acute neurological aetiology for arrest, and odds of mortality was decreased in patients with a preceding chronic respiratory or chronic cardiac condition. This differed from IHCA where a chronic neurological or haematological preceding condition or requirement for renal replacement therapy after PIC admission significantly increased the odds of mortality. Hosmer Lemeshow goodness-of-fit (0.08 and 0.77) and area under the received operating characteristic curve (0.84 and 0.77) for both IHCA and OHCA models respectively were satisfactory, indicating a good model fit and prediction performance.

Table 5-8 Comparison of Resource use in paediatric intensive care for IHCA and OHCA cases

	IHCA N=862	No. died (% group)	OHCA N=841	No. died (% group)	<i>p</i> ^b
Renal replacement therapy	88 (10%)	37 (42%)	29 (3%)	9 (32%)	<0.001
ICP Device	20 (2%)	9 (45%)	32 (4%)	20 (63%)	0.06
Vasoactive drugs	519 (60%)	168 (32%)	505 (60%)	288 (57%)	0.96
ECLS	38 (5%)	16 (42%)	22 (3%)	9 (41%)	0.05

Resource use data missing for 24 IHCA and 14 OHCA. Results expressed as number (percent), missing values were excluded from calculations.

ECLS denotes extracorporeal life support, ICP intracranial pressure monitoring

^b Chi² test or Fishers exact test was used for categorical variable comparing IHCA and OHCA cases.

Table 5-9 Outcomes

	IHCA N=862	OHCA N=841	<i>p</i> ^a
Length of ventilation (LOV) (all)	5 (2-10)	4 (2-7)	<0.001
LOV (survivors)	5 (3-10)	5 (3-9)	0.322
LOV (non-survivors)	2 (1-6)	2 (1-4)	0.908
Length of stay (LOS) in PIC (all)	6 (3-12)	4 (2-8)	<0.001
LOS (survivors)	7 (4-13)	7 (4-11)	0.25
LOS (non-survivors)	2 (1-7)	3 (2-5)	0.687
Mortality at PICU discharge	209 (24%)	423 (50%)	<0.001

Results expressed as days (median: Interquartile range), or number (percent)

^a Chi² test was used for categorical variable and Mann Whitney U test for continuous variables.

Table 5-10 IHCA: Multivariable regression analysis odds of mortality at PIC discharge

IHCA	No. of admissions	No of deaths (% group)	Adjusted odds ratio	95% CI	p value
PIM2 Probability of death	n/a	n/a	8.8	3.8-20.8	<0.001
Two fixed and unreactive pupils	43	36 (84%)	19.17	8.04-45.7	<0.001
Vasoactive drugs	519	168 (32%)	3.20	1.99-5.13	<0.001
Renal replacement therapy	88	37 (42%)	1.95	1.16-3.28	0.011
Chronic neurological Condition	112	39 (26%)	1.9	1.15-3.04	0.012
Chronic haematological Condition	10	6 (60%)	6.99	1.75-27.94	0.006

Variables entered into model: Age (continuous variable), sex, PIM2 (probability of death), all twelve chronic condition groups, all nine acute cause of arrest groups, transferred from secondary hospital, use of ECLS, use of renal replacement therapy, use of vasoactive drugs and presence of two fixed and unreactive pupils on PICU admission

71/862 (8.2%) cases were missing. Hosmer Lemeshow test goodness-of-fit = 0.74
Area under the receiver operating characteristic (ROC) Curve = 0.77 (95%CI: 0.74-0.81)

Table 5-11 OHCA: Multivariable regression analysis odds of mortality at PIC discharge

OHCA	No. of admissions	No of deaths (% group)	Adjusted odds ratio	95% CI	p value
PIM2 Probability of death	all	n/a	10.97	4.68-25.74	<0.001
Two fixed and unreactive pupils	191	183 (96%)	11.63	4.76-28.41	<0.001
Vasoactive drugs on PIC	505	288 (57%)	1.76	1.21-2.56	0.003
Acute neurological aetiology	58	46 (79%)	2.73	1.23-6.07	0.014
Transferred from secondary hospital	621	321 (52%)	1.94	1.23-3.03	0.004
Chronic respiratory condition	108	28 (26%)	0.37	0.21-0.65	0.001
Chronic cardiac condition	160	48 (30%)	0.39	0.25-0.62	0.001

Variables entered into model: Age (continuous variable), sex, PIM2 (probability of death), all twelve chronic condition groups, all nine acute cause of arrest groups, transferred from secondary hospital, use of ECLS, use of renal replacement therapy, use of vasoactive drugs and presence of two fixed and unreactive pupils on PICU admission.

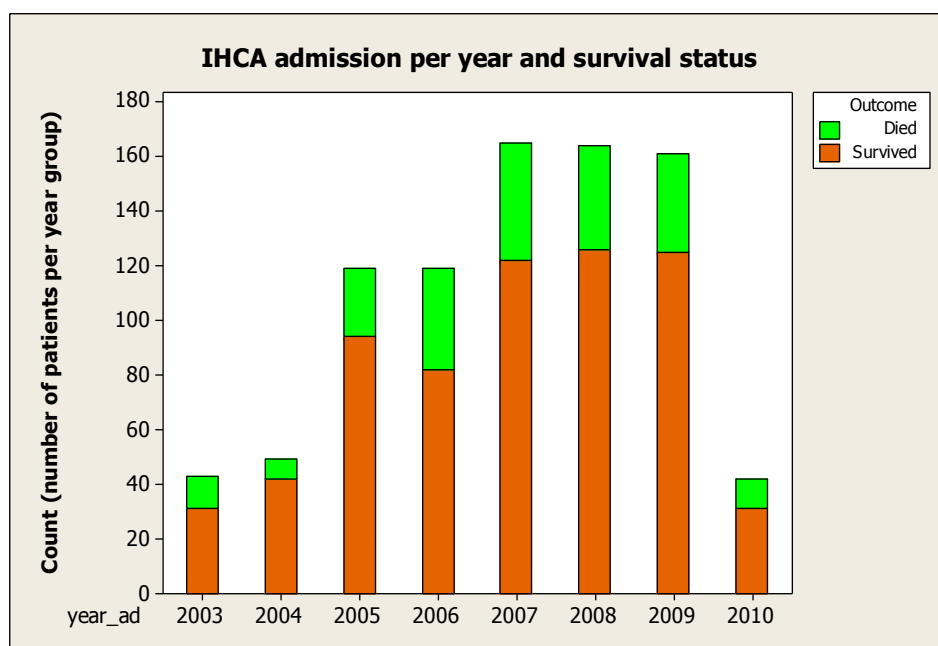
45/841 (5.4%) cases were missing. Hosmer Lemeshow test goodness-of-fit = 0.08
Area under the receiver operating characteristic (ROC) Curve 0.84 (95%CI: 0.81-0.87)

5.5.4 Incidence of children admitted to PICU after cardiac arrest in UK

Figure 5-6 and Figure 5-7 shows a significant step increase in the number of cardiac arrest cases for both IHCA and OHCA coded from the PICANet dataset during the years 2005-6 and 2007-9 although mortality rates remained constant. Sensitivity analysis showed this was not accounted for by the exclusion of the in-PICU arrest patients or the 'other' non-classifiable group. Incidence calculations were therefore performed on the 2007-2009 cohorts only. The 2010 cohort only included available submitted data up to the 1st June; however, the majority of PICUs were at least two months behind on data submission explaining the small number of patients. Therefore this year group was also excluded.

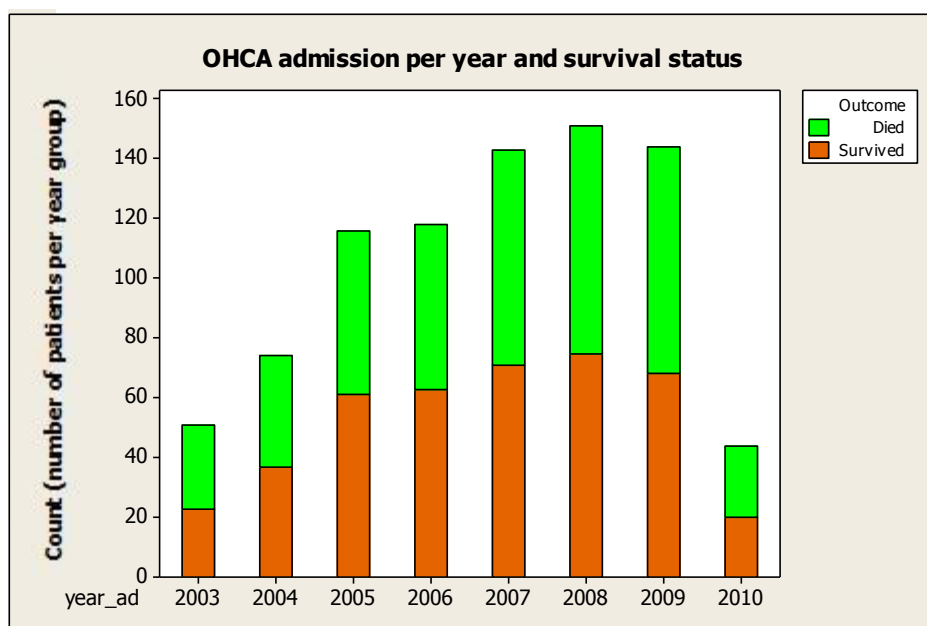
Using national population denominator data from the Office for National Statistics for Great Britain (ONS, 2010), incidence rates for OHCA patients admitted to PICU were calculated (Table 5-12). Overall (0-15yrs) incidence rate was 1.3 per 100,000 person-years (95% CI: 1.0-1.5). Infants (<1 year) had an incidence rate 6.8 times higher than older children (8.9 per 100,000 person-years (95%CI: 6.9-11.3).

Figure 5-6 Number of IHCA cases in PICANet database per year



2010 data submission was incomplete. Only data submitted by the 1st June was available

Figure 5-7 Number of OHCA cases in PICANet database per year



Data submission for 2010 year was incomplete. Only submitted data on 1st June was available.

Table 5-12 Table of Age specific and overall incidence rates of OHCA admitted to PICU per 100,000 UK population per year (2007-2009).

Age Group	Population^a (n)	2007 ^b(rate: 95%CI)	2008 (rate: 95%CI)	2009 (rate: 95%CI)	2007-9^c (rate 95%CI)
<1 year	762700	9.3 (7.2-11.7)	8.7 (6.7-11.0)	8.8 (6.8-11.2)	8.9 (6.9-11.3)
1-4 years	2818000	0.9 (0.6-1.4)	1.3 (0.9-1.8)	1.1 (0.7-1.6)	1.1 (0.7-1.6)
5-10 years	3971570	0.4 (0.2-0.6)	0.4 (0.3-0.8)	0.5 (0.3-0.8)	0.4 (0.3-0.7)
11-15 years	3583593	0.8 (0.2-0.5)	0.7 (0.2-0.5)	0.5 (0.2-0.4)	0.7 (0.2-0.5)
0-15 years	11135863	1.2 (1.0-1.5)	1.3 (1.1-1.6)	1.2 (1.0-1.5)	1.3 (1.0-1.5)

^aAge group and population data from Office of National Statistics (mid 2008 statistics) (ONS, 2010). ^bRates expressed as admissions per 100,000 population (95% confidence interval)

^ccombined average rate for 2007-2009.

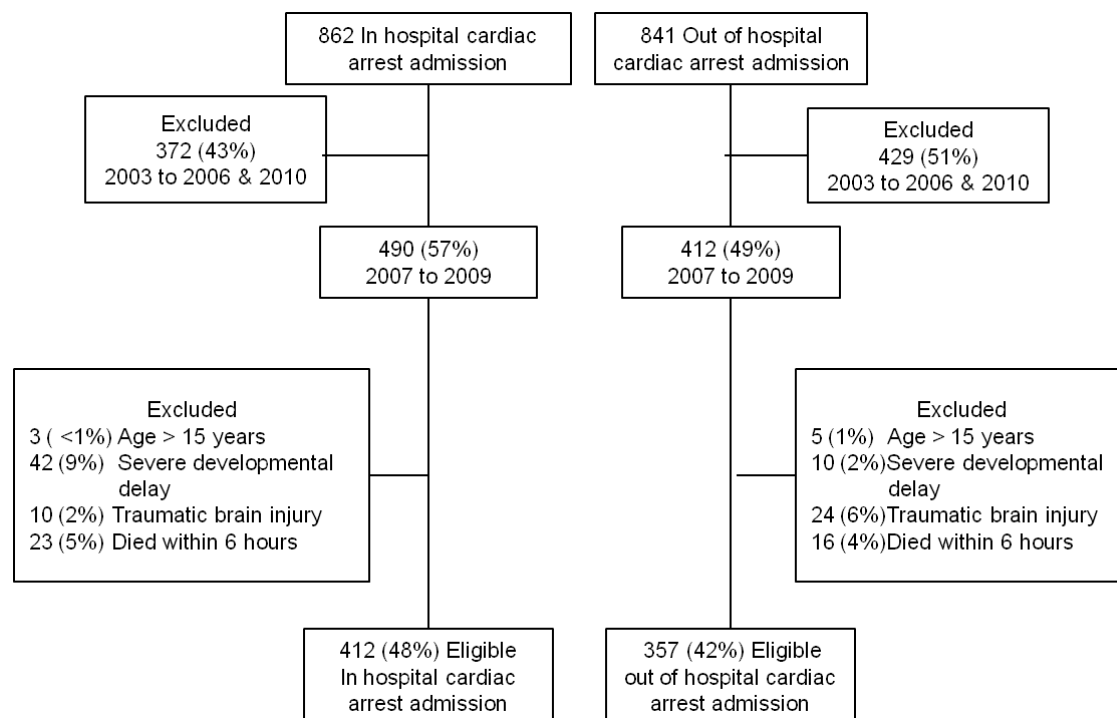
5.5.5 Sample size calculation

Additional exclusion criteria which would be required in a post cardiac arrest interventional study (excluding patients >15 years, following traumatic brain injury or with severe developmental delay on presentation) were applied to the 2007-2009 cohort (Figure 5-8). Figure 5-9 shows the variation of total number of IHCA and OHCA combined admissions to UK and Eire individual PICUs in 2007-2009.

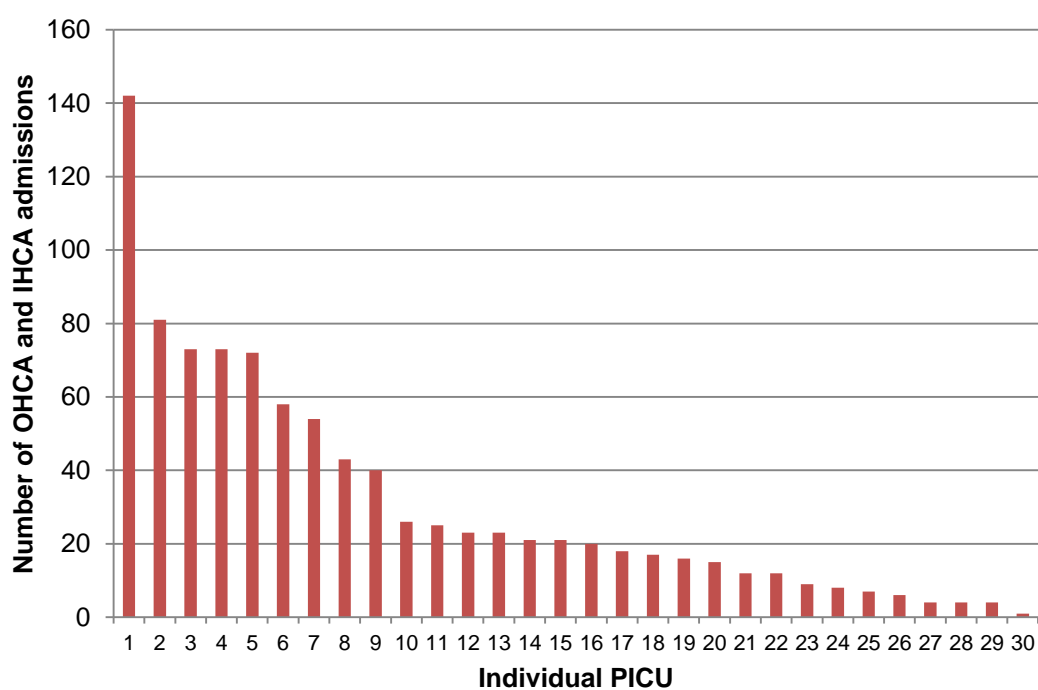
Numbers of admissions per unit were calculated. Table 5-13 shows the potential incremental increase in study size population as the number of 'recruiting' PICUs rises. The top 10 admitting PICUs admitted 80% of the potentially eligible IHCA and 66% OHCA study patients. An addition of 10 further PICUs only increased the proportion of potential patients by 15% for an IHCA study but by a further 28% for an OHCA study.

Finally, using the crude mortality results for IHCA and OHCA patients for the total cohort a sample size calculation grid was created (Table 5-14). Maintaining a two-sided significance level of 0.05 and power of 80% to detect survival as a primary outcome, trial sample size requirements were calculated in order to identify the increased treatment effect size of an intervention (e.g. therapeutic hypothermia). Duration of the trial is presented for increasing the number of recruiting PICUs in the UK (initially assuming 100% inclusion, randomisation and follow up). Therefore, for an OHCA study attempting to assess a 10% absolute increase in treatment effect (50 to 60% survival) with 20 recruiting UK PICUs, 776 patients are required and would take approximately 6.9 years. However, the same treatment effect size assessment (10% absolute increase from 76 to 86%) in IHCA for the same number of recruiting units would take 3.7 years. In reality, refused consent, drop-out rate and loss to follow-up will further reduce the patient population to approximately 50% expected, therefore requiring nearly 14 years to recruit to an OHCA RCT and 7 years for an IHCA RCT.

Figure 5-8 Study flow chart for IHCA and OHCA eligible population for sample size estimation



Exclusion of patients using severe developmental delay (coded as high risk medical diagnosis on PIM2 calculation), trauma and traumatic brain injury cardiac arrest aetiology and death within six hours of PIC admission.

Figure 5-9 Graph of total IHCA and OHCA admissions for individual PICUs (2007-2009)

Individual PICUs ordered by sum total of IHCA and OHCA admission (2007-2009)

Table 5-13 Potential sample population for increasing number of PICUs

No. of PICUs ^a	IHCA in 3 years	IHCA per yr	% total IHCA	OHCA In 3 yrs	OHCA per yr	% total OHCA
8	301	100	73	208	69	58
10	329	110	80	233	78	66
15	365	122	89	292	97	82
20	389	130	95	336	112	94
30	412	137	100	357	119	100

^aRanked PICUs by combined number of IHCA and OHCA admission (2007-2009)

IHCA and OHCA admissions excluding; patients ≥ 16 years, traumatic brain injury aetiology, patients dying within 6 hours of admission and associated severe developmental delay.

Table 5-14 Table of sample size requirement for variable treatment effect size and time to recruit

Baseline group event rate	Treatment group event rate	% effect change	Significance	Power 1-β	Patient number needed in each arm	Total in study	10 PICUs	20 PICUs	30 PICUs
OHCA Primary outcome survival						Time to recruit (years)			
50%	57%	7%	0.05	0.8	796	1592	20.4	14.2	13.4
	60%	10%			388	776	9.9	6.9	6.5
	62%	12%			268	536	6.9	4.8	4.5
	65%	15%			170	340	4.4	3.0	2.9
	70%	20%			93	186	2.4	1.7	1.6
IHCA Primary outcome survival						Time to recruit (years)			
76%	83%	7%	0.05	0.8	521	1042	13.0	8.0	7.6
	86%	10%			241	482	6.0	3.7	3.5
	88%	12%			160	320	4.0	2.5	2.3
	91%	15%			95	190	2.4	1.5	1.4
	92%	20%			47	94	1.2	0.7	0.7

5.6 DISCUSSION

5.6.1 Summary of findings

This is the largest cohort study of paediatric cardiac arrest patients admitted to PICU in the UK. 1.6% of PICU admissions were following cardiac arrest with half of patients aged below one year. Survival rates for patients admitted to PICU after cardiac arrest were significantly higher for IHCA compared to OHCA (76% vs. 50%; $p=0.001$) but also significantly higher than previous published data. We identified important differences in factors associated with survival between these two groups which will be important when considering the planning for a post cardiac arrest interventional trial. However, the estimated population sample size, available for an intervention study, may be too small for the UK realistically to undertake alone.

5.6.2 Survival rates

Previously, survival rates for IHCA patients achieving a ROSC have ranged between 40-50% and after OHCA: 20-40% (Donoghue et al, 2005; Nitta et al, 2011; Young et al, 2004; Meaney et al, 2006; Nadkarni et al, 2006; Tibballs & Kinney, 2006); both considerably lower ranges than the PICU survival rates found in our current study. The closest comparable studies were from the Pediatric Emergency Care Network (PECARN) in the USA (Meert et al, 2009; Moler et al, 2011; Moler et al, 2009). These included patients with duration of cardiac arrest of at least one minute plus sustained ROSC of at least 20 minutes. The reported survival rates were lower: 49% for IHCA and 38% OHCA patients. A number of differences identified between studies populations may help explain this, although there are also limitations in the current dataset which also require consideration. First, in the current study, two unresponsive pupils were strongly associated with increased mortality after both IHCA (Adjusted OR 19.2 (95%CI [8.04-45.7]) and OHCA (Adjusted OR 11.6 (95%CI [4.76-28.41])). Pupil reaction was also strongly associated with survival after both the IHCA and OHCA paediatric PECARN studies although the rates were considerably different. Unresponsive pupils were reported in the current study for only 5% of IHCA and 24% of OHCA patients, compared with 25% and 68% of patients respectively in the PECARN

studies. Unresponsive pupils are often a sign of significant neurological injury, reflecting a major hypoxic ischaemic insult in the context of cardiac arrest. Therefore, the severity of injury experienced by our cohort of patients may have been less than the PECARN study cohort. As the PICANet database is not a cardiac arrest resuscitation database, it does not collect other key factors to assist stratifying and comparing cardiac arrest severity (e.g. length of cardiac arrest, bystander CPR, epinephrine doses etc). The PICANet definition for cardiac arrest was 'a documented absent pulse or the requirement for external cardiac compression', which follows the Utstein cardiac arrest definition 'the cessation of cardiac mechanical activity, determined by the *inability to palpate* a central pulse, unresponsiveness, and apnoea'. (Zaritsky et al, 1995). However, it is possible that patients with 'minor' episodes of cardiac arrest were included, despite the *a priori* inclusion criteria of requiring invasive mechanical ventilation and intubation at PIC admission to attempt to only include more severe cases.

One possible explanation for potentially over-estimating survival, was that survival outcome in the PICANet database was measured at PICU discharge. This is a relatively short time window to assess survival and it is possible that deaths occurred after PICU discharge (for example patients being discharged to hospices for palliative care). Another possibility is that the original coding may have been incorrect and the diagnosis of cardiac arrest was reflecting a past history of arrest and not a current problem, which would lead to a further overestimation of cardiac arrest survival. Sensitivity analysis of survival rates, for only the 64% of patients, where the PIM2 IHCA and OHCA 'cardiac arrest preceding PIC admission' coding boxes were recorded, did not show a difference in survival rate from the total cohort. Therefore, the inclusion of patients with the text diagnosis of cardiac arrest does not appear to account for the higher observed survival rates.

5.6.3 Age

The age distribution of post cardiac arrest patients, with a significant skew to the left, is similar to the overall PICU population admission profile (PICANet, 2010) and compares similarly to the other published paediatric cardiac arrest studies. Donoghue et al (2005), in a systematic review of 41 studies of OHCA, reported 47.5% (1036/2180) of patients in

paediatric OHCA studies were less than 1 year old. Similar to Moler et al (2009), we did not find a relationship between age and OHCA survival. This is perhaps due to the inclusion of only patients with a sustained ROSC and not all cardiac arrest patients. Previous cohort studies of OHCA have included infants failing resuscitation after sudden infant death syndrome, which increases the proportion of deaths in infants (Young & Seidel, 1999; Atkins et al, 2009).

Survival rates for IHCA did vary with age, with the highest survival rates in infants of one month to one year of age. Meaney et al (2006), in a large cohort of paediatric cardiac arrest occurring in the PICU, also identified the same relationship with infants. In their study, survival rates doubled in this age stratum compared to older children. However, this relationship has not previously been shown in patients arresting outside of the PICU. Differences between USA and UK critical care admission criteria and PICU size may mean that a proportion of the patients having an in-hospital arrest in our study would have been managed in a critical care environment in the USA. For example, 40% of patients in the study by Meaney et al (2006) were not mechanically ventilated and therefore may not have been cared for on a PICU in the UK.

5.6.4 Chronic condition.

A significant proportion of paediatric patients suffering cardiac arrest have associated co-morbidities. Through a re-classification of the diagnostic coding in the PICANet database, we were able to report 79% of IHCA patients and 48% of OHCA had at least one chronic condition (Table 5-4). Moler et al (2009) in a multicentre retrospective study, collected data on 353 IHCA and 138 OHCA patients and reported very similar proportions of one or more chronic conditions in 88% of IHCA and 49% of OHCA. In their comparative study of survivors and non-survivors after IHCA only (Meert et al, 2009), there was an equal proportion with chronic conditions; however, the combined group with haematological, oncological or immunological chronic conditions had an increased odds of mortality (OR 2.61 (95%CI [1.27-5.35])). In our study, through multivariate logistic regression, a chronic respiratory or chronic cardiac condition was in fact associated with improved survival after OHCA.

A cautious approach to interpretation of the relevance of having a chronic condition is required. Absence of a chronic condition was also associated with a higher mortality; however, further analysis showed that this group of patients presented more frequently with aetiologies associated with higher mortality rates which is a more likely explanation than chronic conditions having a 'protective' effect on outcome. Also the relationship of the chronic condition and the actual cause of arrest were not ascertainable in this dataset.

5.6.5 Aetiology of cardiac arrest

When comparing the cause of arrest identified in this study with previous studies, certain considerations are required. There is significant variation in the coding strategies used for allocating cause of arrest of IHCA and OHCA patients. Large IHCA resuscitation registry databases use codes for preceding physiological derangements (e.g. hypotension, metabolic disturbance etc), or associations with post surgical complications (Meaney et al, 2006), whereas OHCA studies tend to allocate on clear diagnostic events (e.g. drowning, poisoning, asphyxia etc). Allocation can be made solely on the assessment of immediate Emergency Medical Service personnel at the scene without additional hospital data (Atkins et al, 2009), or using enhanced data accuracy with national Coroners' data (Deasy et al, 2011a). However, when these two methods are compared they often poorly correlate (Ong et al, 2007; Ong et al, 2006). Finally, variation in the upper age limits of studies can also skew incidence rates for diagnoses more common in adolescents and young adults. For example two OHCA reports by Deasy and colleagues from Melbourne reported incidence of hanging in 0 to 15 years old as 5% (9/193) (Deasy et al, 2010), however, in a similar time period, reported incidence in 0 to 18 year olds of 8% (53/680) (Deasy et al, 2012).

Owing to the inherent limitations of the PICANet dataset, allocation of aetiology for both groups was difficult, resulting in 62% of IHCA and 48% of OHCA causes being unknown. These rates are similar to the unknown diagnosis rate of 67% in the OHCA study by Atkins et al (2009); however, other large OHCA reports have reported less than 7% missing or unknown cause (Young et al, 2004; Herlitz et al, 2007; Moler et al, 2009; Deasy et al, 2010). Allocation of arrest aetiology was easier in older children and where 'events' were identified, such as episodes of trauma, hanging or drowning. This explains the low allocation to IHCA

events as medical deterioration descriptions were often not recorded in the PICANet data. Even where diagnoses such as 'drowning' were documented, the potential for other causes to have precipitated drowning (e.g. epilepsy, arrhythmias and long-QT syndrome), and were not coded, remains possible (Quan & Cummings, 2003; Diekema et al, 1993; Bradley et al, 1999).

Acknowledging the limitations of the dataset, there were a number of important findings in the OHCA group. Age related differences in arrest secondary to hanging or strangulation, cardiac cause, toxin ingestion and near-drowning were noted. Hanging or strangulation occurred in 3% (28/841) of cases overall, but was more common in the 12 to 17 year age stratum, occurring in 12% (16/136). Although it was not frequently documented whether it was deliberate or accidental, it is known that hanging is a common method of attempted suicide resulting in death of adolescents in the UK (Pearson, 2008). Whereas, the four identified patients aged one to four years who arrested secondary to hanging are more likely to have been accidental. The mortality rate for this cause of death was 68% overall. Deasy et al (2012) reported on 53 (8% of 680 patients) cases of hanging related OHCA. ROSC was only achieved in 13% (7/53), of which 43% (3/7) died, with only one survivor neurologically intact. Our current cohort is the largest study of children achieving ROSC after hanging related OHCA and we identified a higher mortality rate than previously reported.

Mortality rates were marginally lower than the overall average for patients after near-drowning (46%; 28/61). Near-drowning occurred in 7% (61/841) of cases and was much more common in the one to four year age stratum accounting for 26% (42/162) of cases in that group. Near-drowning as a proportion of OHCA aetiology has generally been reported between 5-12% (Young et al, 2004; Herlitz et al, 2007; Deasy et al, 2010), although Moler et al (2009) identified near-drowning as a cause in 31% (43/138) of OHCA cases where ROSC for greater than 20 minutes was obtained. Perhaps this reflected a higher ability to successfully resuscitate these children compared to other aetiologies (Young et al, 2004) or a variation in frequency of near drowning rate by geography and climate (Peden & McGee, 2003). However, drowning remains the second commonest cause of unintentional death

after road traffic accidents in young children and an essential group of patients in which to investigate therapies to reduce neurological injuries (Salomez & Vincent, 2004).

In summary, this study identified important variations across age strata of the frequency and survival rates of cardiac arrest aetiologies after OHCA. Limitations of the dataset prevented confident analysis of the IHCA cause of arrest and non-trauma related OHCA causes; however, this study identifies the mixed heterogeneous population presenting to PICU after both IHCA and OHCA and the inherent impact on crude survival rates. This information justifies the separation of IHCA and OHCA populations when assessing interventions on outcome. Even within IHCA and OHCA populations there is considerable heterogeneity which will require consideration in future trial design and analysis.

5.6.6 Requirement for transportation

Transportation from another hospital for PIC admission occurred for 76% of OHCA and 48% of IHCA patients. Risk-adjusted mortality rate (using PIM2) increased for patients admitted from another hospital compared with admission to the hospital co-located with the PICU after OHCA but not IHCA. This contrasts with a much larger review of the use of specialist retrieval teams in the UK also using the PICANet database (Ramnarayan et al, 2010). The study identified that risk-adjusted mortality was lower for patients admitted from other hospitals versus those from within the same hospital (OR 0.65 95%CI [0.53-0.80]) although this included all emergency unplanned admissions and not only post cardiac arrest patients. A possible explanation for this observed difference is that following centralisation of paediatric critical care services, the majority of PICUs are co-located in specialist children's hospital (Pearson et al, 2001). The presence of a PICU co-located and specialist, paediatric trained, emergency department staff may give an advantage to patients admitted after OHCA directly to a large children's hospital. Conversely, limited exposure and reduced skills in advanced paediatric resuscitation in smaller district general hospitals may lead to suboptimal resuscitation of OHCA patients. This important finding warrants further evaluation of confounding factors (e.g. casemix) and may indicate an important area in which to target paediatric cardiac arrest resuscitation training.

5.6.7 PICU intervention

The use of renal replacement therapy was independently associated with a worse outcome after IHCA (OR 1.95 (95%CI [1.16-3.3]) although it was only used in 10% of IHCA and even less frequently after OHCA (3%). Renal replacement therapy is used infrequently after paediatric cardiac arrest. Moler et al (2009) also reported only 5% use after IHCA and 0% for the OHCA. Its minimal use may reflect the perceived futility of treatment in many post cardiac arrest patients, or that renal function in children may be preserved even after significant ischaemia reperfusion injury to other vital organs. However, it has been suggested that high volume continuous veno-venous haemofiltration (one form of renal replacement therapy) may be beneficial in treating the post cardiac arrest syndrome (Nolan et al, 2008) or, as an alternative to cardiopulmonary bypass or ECLS, for rewarming after extreme hypothermia (Alfonzo et al, 2009). Also, its use after baseline characteristic adjustment in conjunction with and without therapeutic hypothermia was found to improve six month survival outcome in a study of 88 adult VF cardiac arrest patients (Odds ratio 4.4 (95%CI [1.1-16.6]) (Laurent et al, 2005). Therefore, although its use in a small proportion of patients in this study was associated with worse outcome there may be a future role for renal replacement therapy in treating post-cardiac arrest patients and its use in an interventional study should be closely monitored and carefully protocolised.

5.6.8 Length of stay and ventilation

Length of stay in PICU is shorter after OHCA than IHCA. However, survivors and non-survivors length of stay and length of invasive ventilation was similar between IHCA and OHCA. Meert et al (2009) reported that PIC length of stay was 15 (IQR [6-28]) days for survivors versus 6 (IQR [1.0-27]) days for non-survivors. This is twice as long as the length of stay reported in the current study (IHCA survivors: 7 (IQR [4-13]) versus non-survivors: 2 (IQR [1-7] days). Multiple factors may account for this observed difference. The higher survival rates in our study may be due to lower illness severity for IHCA patients and length of stay may reflect this. However, UK and USA critical care bed numbers and usage also differ (Wunsch et al, 2011). Therefore discharge practice variation may be an explanation (i.e. earlier discharge to the ward area in the UK). Unfortunately, owing to the lack of data on

length of hospital stay in our study we are unable to compare time to hospital discharge. For non-survivors, a difference in clinical practice regarding length of time before withdrawal of intensive care in patients with devastating injury after cardiac arrest may also be an explanation; unfortunately this level of data is also missing. Overall length of stay for OHCA patients is similar to the US data (Moler et al, 2009); however, no breakdown of length of stay for survivors and non-survivors is given specific to OHCA patients and therefore cannot be compared (Moler et al, 2011).

Length of invasive ventilation is relevant, when considering the impact of a post-cardiac arrest interventional study of therapeutic hypothermia, as invasive ventilation will be required throughout the process of hypothermia until rewarming. Median length of invasive ventilation was two days shorter than PIC length of stay for both IHCA and OHCA patients. Durations of 24-72 hours of therapeutic hypothermia have been previously used in clinical trials with a requirement of an additional 18-24 hours of ventilation during the rewarming phase. The impact this may have on our reported length of ventilation for current survivors may be minimal, as the median length of stay after IHCA and OHCA is five days. However, for non-survivors there may be a significant increase. Length of ventilation for non-survivors was 2 (IQR [1-6]) days after IHCA and 2 (IQR [1-4]) days after OHCA. A proportion of patients die within the first 12-24 hours of PIC admission due to cardiac and respiratory deterioration; however, a significant proportion of patients' deaths are associated with withdrawal of intensive care after neurological assessment. This is a group of patients that therapeutic hypothermia may potentially benefit; however, the therapy will prolong length of ventilation and time to neurological assessment (as the patient is required to have reached normothermia prior to this). In this study, the use of therapeutic hypothermia following cardiac arrest was not recorded although following the survey of practice of PIC consultants described in Chapter 4, its use was likely to have been infrequent during 2003-2008. However, regardless of current clinical use of therapeutic hypothermia, a randomised controlled trial treatment protocol would increase the length of ventilation and resultant PICU stay in a proportion of survivors and non-survivors. The health care cost of increased PICU care and the emotional effect on families as a result of therapeutic hypothermia is therefore

an essential component requiring investigation through health economic and qualitative analysis alongside a clinical efficacy study.

5.6.9 Incidence rates

We identified an overall incident rate of OHCA with ROSC admitted to PICU of 1.3 (95%CI [1.0-1.5]) children per 100,000 person-years in the UK, with a seven fold increase in the under one year olds (8.9 (95%CI [6.9-11.3])). Comparison with other studies is difficult as previous incidence figures have been published representing the total cardiac arrest population including patients failing to achieve ROSC. In the USA, OHCA incidence is 8 per 100,000 person-years (Atkins et al, 2009) with infants (less than 1 year) having a nine fold increase (72 per 100,000 person-years). This is similar to a smaller study from Helsinki where the rates of OHCA including all patients were 9.8 per 100,000 person-years (Kuisma et al, 1995) and a more recent Japanese OHCA registry study reporting 7.3 per 100,000 person-years (Nitta et al, 2011). However, a study in Melbourne reported an incidence of only 5 per 100,000 person-years for the same age range (Deasy et al, 2010).

Without knowledge of the UK total incidence rate of cardiac arrest in children, extrapolation of the identified rate to the total population is speculative. If our OHCA rates were similar to USA rates then this equates to a 16% ROSC rate to achieve the incidence rate quoted, whereas, compared to the Melbourne data, our ROSC rate would be 26%, closer to the rate calculated in the meta-analysis of OHCA studies (Donoghue et al, 2005). Similar to Atkins et al (2009), we identified a significant increased incidence in the under ones. However, the increase identified was smaller (seven versus nine times) and likely to reflect the high proportion of infants with sudden infant deaths syndrome who fail to be resuscitated in their study and were not included in ours.

IHCA incidence figures were not calculated owing to difficulty obtaining accurate denominator data from the Hospital Episode Statistics database (HES, 2012) and because of the exclusion of cardiac arrests occurring within PICU after admission. Accurate assessment of IHCA rates have been identified as problems globally, with few paediatric or adult published studies (Merchant et al, 2012; Sandroni et al, 2007). The exception is the study by Tibballs et al (2006) who reported a rate of IHCA of 1.06 per 1000 hospital

admissions from a single centre study. Improved information may be available in the future with initiatives such as the National Cardiac Arrest Audit in the UK (ICNARC, 2012). However, only the total numbers of cardiac arrest admissions to PICU, rather than population rates, are available in the current study to assist trial sample size estimations, although the inclusive coverage of the all UK PICUs significantly reduces the risk of estimate inaccuracies and bias.

5.6.10 Sample size calculation

Sample size calculations for randomised controlled trials are recommended by international CONSORT guidelines (ICH, 1999; Moher et al, 2001); ethically important (Altman, 1980) although at best an educated guess (Charles et al, 2009; Schulz & Grimes, 2005). They are required to identify whether the hypothesis test has a good chance of showing a desired difference (if it exists), demonstrating the study has a chance of obtaining conclusive results whilst utilising only a reasonable amount of resources (e.g. money and time). Important pre-requisites are required, including: that the study sample comes from the same or similar populations to the pilot study population, the population of interest is not changing over time and that a desired difference exists. Regarding these assumptions, the PICANet data are an attempt to minimize the difference between pilot and sample study population and the cardiac arrest population does not appear to be changing over recent years. However, the potential impact of new treatments (e.g. therapeutic hypothermia) has not formally been assessed in this study. The existence of a desired treatment effect is not conclusive. On the one hand, adult cardiac arrest studies have demonstrated an absolute reduction in mortality with therapeutic hypothermia of 16% (33% to 55%) (HACA, 2002) and 23% (26% to 49%) (Bernard et al, 2002) survival with good neurological outcome. On the other, no observational study has yet demonstrated a beneficial (or harmful) effect in children (Fink et al, 2010; Doherty et al, 2009). Within the constraints of these assumptions, we undertook a sample size estimation calculation using the PICANet data.

Using the survival event rates for IHCA and OHCA patients, a range of potential treatment effect sizes for therapeutic hypothermia with calculated study sample sizes has been presented. The length of time to recruit the number of patients has also been calculated

using individual unit cardiac arrest admission rates, albeit using the assumption of 100% recruitment and follow up. Unfortunately, this final assumption is the most challenging and has the highest risk of altering the number of available patients and duration of trial length. The two therapeutic hypothermia studies in the USA (NCT00878644; NCT00880087) are currently only randomising one in seven patients presenting after both IHCA and OHCA, owing to inclusion and exclusion criteria, informed consent procedures and arriving to PICU within the six hour time window (Personal communication: F. Moler Chief Investigator (March 2011)). Included in the sample size population we excluded patients with severe developmental delay and cardiac arrest secondary to trauma; however, there are likely to be more exclusion criteria in the main study. Information regarding time to admission to PICU after cardiac arrest is not available and potential delays making patients ineligible for a study are not known. The use of informed consent or the use of deferred consent may also impact on recruitment, although the use of deferred consent in paediatric emergency medicine is still novel and lessons from the only on-going trial using this consent method are still awaited (NCT01029717). However, even with an optimistic ratio of 50% identified patients being entered into a study due to refused consent or failure to recruit, the UK would require funding for nearly 14 years to recruit to an OHCA study and 7.5 years for an IHCA study using 20 PICUs to demonstrate a 10% absolute difference in outcome.

A prospective pilot study with appropriate inclusion and exclusion criteria, consent processes and treatment protocols is therefore an essential component to minimise the variability and assumptions presented here. It would also allow a more accurate estimation of the potential treatment effect of therapeutic hypothermia in the paediatric population and consider justification for further investment in a definitive and costly phase three clinical trial. Even with this information, our estimations would be that the UK is too small to have sufficient patients for timely recruitment and therefore international collaboration would need to be explored.

5.6.11 Limitations

The strength of this study, through the use of the PICANet database, is that complete national coverage of patients admitted to all 30 PICUs in UK and Eire is achieved. Robust

internal validation checks occurred and data monitoring procedure aimed to limit error and potential bias (PICANet, 2010). However, this study does have some inherent weaknesses. As previously mentioned, the most important is that PICANet database is not a primary cardiac arrest database or registry. Although PICANet uses a modification of the Utstein defined definition for cardiac arrest and has clear guidance for coding in the primary dataset allocation to either IHCA or OHCA prior to PICU admission, this was missing in 36% of cases and led to the inability to allocate 11% (308/2812) to any of the three cardiac arrest groups, potentially introducing case-selection bias and resulting in an underestimation of the population sizes.

Survival outcomes were significantly higher than previously reported. Overestimation of both IHCA and OHCA rates due to short follow up time, missing data and potentially inclusion of patients who were not admitted immediately after a cardiac arrest is possible. Use of these elevated survival rates in the sample size calculation will also affect the number of patients required to show the same absolute treatment effect; however, even using the previously published survival rates by Moler et al (2009), the overall conclusion that both trials would take in excess of seven years is not altered.

We excluded in-PICU arrest from analysis. These patients would be potentially eligible for inclusion and therefore increase the numbers in an IHCA study. Future analysis of this population may be possible as more UK PICUs submit validated PCCMDS data.

PICANet does not record Utstein defined resuscitation information such as length of cardiac arrest, presenting cardiac rhythm, doses of epinephrine etc (Jacobs et al, 2004; Zaritsky et al, 1995). Therefore, the multiple logistic regression models presented in this study lack important confounding factors needed for case adjustment. Further in depth evaluation of this level of clinical detail is required to develop and validate accurate prediction models for these populations and would allow an assessment of the severity of cardiac arrest in relationship to outcome. In addition PICANet only collects complete data to PICU discharge. Hospital discharge data is collected but often incomplete and neurological outcome data are not part of the PICANet dataset. Therefore the outcome data presented here only represents a short survival outcome and may overestimate longer term survival.

The coding of chronic conditions and causes of cardiac arrest were undertaken systematically; however, conditions may have fallen into both an acute and chronic diagnosis or occurred after the primary cardiac arrest and rely on accuracy of original data entry. These difficulties with identifying diseases in electronic health records has been previously recognised and further validation of the findings presented in this study are required (Manuel et al, 2010).

Finally, sample size calculations have been estimated here using the effect of the treatment on survival as the primary outcome. This was required as no neurological outcome data was collected. All previous therapeutic hypothermia studies in adults after cardiac arrest and neonates after hypoxic ischaemic encephalopathy have used the combined outcome of death and severe neurological disability. This composite outcome has reported increased effect size changes compared to survival alone (Chapter 1, Table 1-5). A re-evaluation of a potential treatment effect size will be required in a future pilot study, collecting both survival and neurological outcome data.

5.7 CONCLUSION

This is the largest cohort study of paediatric cardiac arrest patients admitted to PICU in the UK. 1.6% of PICU admissions were following cardiac arrest with half of patients aged below one year. Survival rates for patients admitted to PICU after cardiac arrest were significantly higher for IHCA compared to OHCA (76% vs. 50%) but also significantly higher than previous published data. We identified important differences in factors associated with survival and case mix between these two groups, supporting the need for two separate trials. However, the estimated population sample size, available for an intervention study, may be too small for the UK to realistically undertake alone and so require international collaboration. Limitations of this study have been presented including the lack of resuscitation specific patient data, neurological outcome data and potential case selection bias.

Table 5-15 Chapter 5 and RCT feasibility

What have we learnt from this study towards the feasibility of a UK randomised controlled trial?

Survival rates in children admitted to PICU after cardiac arrest are significantly higher for arrests occurring in-hospital and separation of IHCA and OHCA patients in a trial is recommended.

Two unresponsive pupils, the use of vasoactive drugs, presence of certain chronic conditions or transfer from another hospital to PICU are all important factors affecting survival after IHCA and OHCA

Length of ventilation and stay on PICU may be prolonged for patients receiving therapeutic hypothermia in the context of an intervention trial with health care cost implications.

Cardiac arrest rates and estimation of required study sample size for an intervention study indicates that the UK would not be able to perform the trial without international collaboration.

5.8 ACKNOWLEDGEMENT

PICANet is funded by the National Clinical Audit and Patient Outcomes Programme through Healthcare Quality Improvement Partnership, Health Commission Wales Specialised Services, National Health Service (NHS) Lothian and National Service Division NHS Scotland, the Royal Belfast Hospital for Sick Children, and the Pan Thames PICU Commissioning Consortium. We thank all the staff in participating hospitals who gathered data for PICANet. A full list of participating PICUs and steering group and clinical advisory group membership is available on the latest PICANet Annual Report.

<http://www.picanet.org.uk/Documents/General/Annual%20Report%202010/2010%20PICANet%20Annual%20Report.pdf>.

We thank Dr Philip McShane for extracting the study data from the PICANet database and Dr Paul Davies for his statistical advice and guidance.

5.9 CONTRIBUTORSHIP

Dr Scholefield designed the current study protocol, created the new database, re-coded and cleaned data, performed all statistical analysis and drafted study manuscript. Study design and Interpretation of data was performed with supervisory assistance from Drs Morris & Duncan, Profs Gao-Smith & Perkins and with external advice from Dr Parslow (University of Leeds and PICANet) and Prof Tasker (University of Cambridge and Harvard Medical School). Dr Paul Davies provided statistical advice. Dr McShane performed extraction of the primary dataset from the PICANet database with full guidance from Dr Scholefield.

6 Predictive factors for survival to PICU discharge after paediatric out-of-hospital cardiac arrest: A UK multicentre, retrospective, cohort study.

“Prediction is very difficult, especially if it’s about the future!”

Thomas Alva Edison (American Inventor, born 1847)

6.1 ABSTRACT

6.1.1 Introduction

Despite initial successful resuscitation after paediatric out-of-hospital cardiac arrest (OHCA), a large proportion of patients will not survive to PICU or hospital discharge. Accurate prediction of likely survivors or patients at high risk of mortality is of benefit to clinicians, when choosing appropriate patient care and counselling families; and to researchers targeting interventional studies on patients most likely to benefit from therapies or for risk-stratified randomisation. However, no OHCA data to formulate prediction currently exists with respect to the UK paediatric population.

6.1.2 Aims

To identify predictive factors for survival to PICU discharge, available at the time of resuscitation or at admission to PICU, in children achieving a return of spontaneous circulation after OHCA.

6.1.3 Method

A retrospective, multi-centre, cohort study of infants (older than 24 hours) and children (before their 16th birthday) admitted to three large UK PICUs after OHCA over a seven year period (Jan 2004- Dec 2010) was performed. Identified variables, associated with PIC survival, were analysed and included in a multivariate logistic regression model and Correlation and Regression Tree (CART) analysis to create a prediction tool.

6.1.4 Results

One hundred and fifty five OHCA patients met study entry criteria. 32% (50/155) survived to PIC discharge. Age, bystander CPR and witnessing of arrest were not associated with survival. Factors available before or during resuscitation, associated with increased survival, included; presenting in a rhythm that can be cardioverted (referred to as a 'shockable rhythm' i.e. ventricular fibrillation or ventricular tachycardia), shorter duration of cardiac arrest, return of spontaneous cardiac output prior to arrival in the emergency department and lower number of epinephrine doses. Additional factors associated with survival and

available within four hours of PICU admission included; higher blood pH, lower blood lactate, lower maximum blood glucose, higher arterial base excess, lower Paediatric Index of Mortality (PIM2) score and two reactive pupils. A multivariate logistic regression model with factors available before and during resuscitation identified presenting in a shockable rhythm as strongly associated with survival. Including factors available up to four hours after PIC admission identified raised blood lactate and two unresponsive pupils as strong predictors of mortality. A decision tree identifying patients with high risk of mortality was created using both regression coefficients and CART analysis.

6.1.5 Conclusion

This study has identified multiple factors associated with survival after return of spontaneous circulation in UK children after OHCA. Two unresponsive pupils and raised lactate within four hours of PIC admission remained strong predictors after multivariate logistic regression and CART analysis for mortality. This information will be of value in determining potential inclusion and exclusion criteria for an intervention trial and could be considered as a tool for risk-stratified randomisation within a RCT of therapeutic hypothermia after cardiac arrest.

6.2 INTRODUCTION

Survival rates for children after out-of-hospital cardiac arrest (OHCA) are generally poor, although vary widely in the published literature (Donoghue et al, 2005; Young et al, 2004; Deasy et al, 2010; Atkins et al, 2009). The heterogeneity of cardiac arrest aetiologies within studies and cardiac arrest definitions between studies are some of the major causes for this variation. Attempts to standardise resuscitation reporting in studies, by adoption of the Utstein template, have resulted in some improvement (Zaritsky et al, 1995). However, most studies are small case series or include all patients suffering cardiac arrest and report only a small proportion with return of spontaneous circulation (ROSC). Therefore, in addition to variations in outcome definitions and paediatric populations outside the UK, these limitations reduce the ability to use currently reported outcome rates to plan a UK post cardiac arrest therapeutic intervention clinical trial (e.g. the use of therapeutic hypothermia after OHCA).

Prediction of survival or mortality after OHCA is of importance to both clinicians caring for patients and to researchers designing clinical trials. The ability to predict outcome for individual patients can help clinical decision making regarding therapeutic options or whether continued therapy may be futile, thereby assisting in the counselling of parents and families. Researchers can use prediction tools in a similar way but for a different purpose. The inclusion of patients in a clinical trial with very high or very low risk of survival, who are likely to survive or die irrespective of any therapeutic intervention, risks masking the beneficial or harmful effects of a therapy. Critical care, randomised controlled trials have repeatedly struggled with the problems of heterogeneity in study populations resulting in a low signal (meaningful information) to noise (unwanted signal) ratio and resulting in no effect from the intervention despite often strong evidence from pre-clinical, observational and single centre randomised controlled trials (Vincent, 2010). Focusing the study population on a group who are most likely to benefit from the therapy is one approach to improve this. Therefore, understanding the potential study population and identifying key factors which may be useful inclusion or exclusion criteria and may allow more efficient research into a targeted population (Vincent et al, 2010). However, a downside to this approach is the risk of targeting sub-populations which are too small and not reflective of the general ICU

population. The results of the study may therefore fail to be generally applicable. A relevant example of this is the European Hypothermia After Cardiac Arrest (HACA) trial which identified a positive effect of therapeutic hypothermia in adult OHCA patients presenting in a shockable rhythm (HACA, 2002). A criticism of the study, and potential reason for slow uptake of the therapy over the 10 year period since publication was that only 8% of the total screened OHCA population was included in the study. Therefore, the therapy was not tested on the majority (92%) of OHCA patients presenting to these ICUs. A potential second approach to using prediction tools in research could be to use the knowledge of strong predictive factors in stratifying populations in an RCT either at the outset, before randomisation or during a risk-stratified analysis of the RCT outcome (Kent & Hayward, 2007). This would enable a balance of the final comparative populations and in addition, increase the power to detect subgroups of patients who are likely to benefit or be harmed by the intervention (Hayward et al, 2006; Kent & Hayward, 2007)

There have been considerable efforts to identify important prediction factors in children after OHCA over the last few decades. Various factors predicting mortality have been reported from observational studies including; prolonged duration of cardiac arrest (Schindler et al, 1996; Suominen et al, 1997; Young et al, 2004), no ROSC at scene or resuscitation required after arrival to the emergency department (O'Rourke, 1986; Ronco et al, 1995; Sirbaugh et al, 1999; Moler et al, 2011), no-bystander CPR (Abe et al, 2012), arrest not witnessed (Atkins et al, 2009; Donoghue et al, 2005), age (Engdahl et al, 2003), increased number of doses of epinephrine (Schindler et al, 1996; Young et al, 2004), presenting in a non-shockable rhythm (Mogayzel et al, 1995; Atkins et al, 2009; Moler et al, 2011) and in the setting of cardiac arrest associated with trauma. However, no single factor or combination of factors in the paediatric population has been incorporated into a prediction rule for either guaranteed survival or termination of resuscitation. In addition, over time, prediction factors have changed. For example, in the 1980s, Zaristky et al (1987) and Gillis et al (1986) reported survival futility if CPR duration was greater than 10 minutes and 15 minutes respectively. By the 1990s Schindler et al (1996) extended the time duration considered futile to greater than 20 minutes of CPR in the emergency department, and in the 2000s Young et al (2004) reported that CPR greater than 31 minutes in the emergency department

was deemed futile. There have been attempts in the adult population to create termination of resuscitation rules using large sample sizes in retrospective studies and included combinations such as: witnessing of the arrest by emergency medical personnel, the lack of need for cardiac defibrillation and lack of return of spontaneous output out-of hospital (Morrison et al, 2006; Morrison et al, 2007; Sasson et al, 2008). However, even in the adult OHCA population, as the quality of pre-hospital resuscitation improves (Margey et al, 2011), experimental neuroprotective interventions such as therapeutic hypothermia during CPR are explored (Bernard et al, 2010) and further data on the outcome variability between individual centres and countries emerge (Berdowski et al, 2010; Nichol et al, 2008b), these rules also become less and less precise as time moves on.

Moler et al (2011) published the only large multicentre cohort study investigating a population of post-OHCA children with ROSC and admission to PICU. This study was funded and performed by the large Pediatric Emergency Care Applied Research Network (PECARN) in the USA and aimed to describe patient and cardiac arrest event characteristics after OHCA and early hospital management. In addition they sought to identify factors most strongly associated with hospital survival which they subsequently used in designing the Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA) studies (NCT00878644; NCT00880087). Over a period of 18 months, 138 OHCA patients from 15 sites were included. Survival rate to hospital discharge was 38% (53/138). The event characteristics most associated with survival included; weekend arrest, cardiopulmonary resuscitation not on-going at hospital arrival, arrest rhythm not asystole, shorter duration of cardiac arrest, and drowning or asphyxial arrest event. Additional factors available in the first 12 hours post resuscitation associated with survival included: absence of vasopressor or inotropic support, higher body temperature, higher pH, lower lactate, lower maximum glucose, and normal pupillary response. In a multivariate logistic regression analysis of factors available during or immediately after resuscitation, after accounting for age, gender, race and presenting cardiac rhythm, they found the administration of atropine or epinephrine to be associated with increased mortality. A second model which included post-resuscitation factors identified; pre-existing lung or airway disease, aetiology of drowning or asphyxia, higher pH and two reactive pupils to be associated with lower mortality. However, duration of cardiac arrest and

lactate levels were excluded from both multivariate analyses due to missing data. Although this study does give valuable information regarding the post-OHCA population, potential differences between the UK and USA may exist. These include; the patient population, aetiology of cardiac arrest, healthcare provision, choices of intensive care therapies and approaches to palliative and end of life care (Wunsch et al, 2011).

The Paediatric Intensive Care Audit Network (PICANet) database, as detailed in chapter five, allowed useful epidemiological assessment of the UK post-cardiac arrest population admitted to PICUs and identified that the survival to PICU discharge for patients admitted to PICU after OHCA was 50%. However, the ability to investigate resuscitation specific factors was severely limited as these were not included in the collected dataset. It was not possible to assess the sensitivity and specificity of the matrix model by checking primary records which was a potential limitation due to the unexplained high survival rate in relationship to other published studies and there were concerns regarding the accuracy and interpretation of the coding system for chronic conditions and acute aetiologies of arrest. Therefore, we designed a retrospective study to investigate the UK post-OHCA population admitted to PICU collecting Utstein defined resuscitation factors and additional key physiological parameters to allow the creation of a prediction tool. The findings of this study will assist the methodological design of a randomised controlled intervention study by potentially identifying key factors for patient inclusion and exclusion, and identifying potential stratification/minimisation criteria for randomisation.

6.3 AIMS

6.3.1 Primary Aims

1. To identify predictive factors for survival to PICU discharge in children who are admitted to PICU after out-of hospital cardiac arrest in the UK.

6.3.2 Secondary Aims

1. Ascertain the survival to PICU discharge rate of children who are admitted to PICU following out-of-hospital cardiac arrest.
2. Develop a risk prediction tool utilising preceding or during resuscitation factors associated with survival.
3. Develop a risk prediction tool utilising factors available at the time of PICU admission associated with survival.

6.4 METHODOLOGY

6.4.1 Settings and participants

This retrospective, multi-centre, cohort study included infants and children admitted to PICU after out-of-hospital cardiac arrest (OHCA) over a seven year period (January 2004 to December 2010). Patients were identified from admission records to the three Paediatric Intensive Care Units (PICUs) of Birmingham Children's Hospital (BCH), Alder Hey Children's Hospital (ACH), Liverpool and Great Ormond Street Hospital (GOSH), London. All three are large, regional paediatric centres admitting 1100-1700 infants and children per year on to PICU, accounting for 23% of all UK PICU annual admissions (PICANet, 2010). National and local databases identified potentially eligible patients. These included the PICANet admission coding for preceding cardiopulmonary resuscitation and preceding out-of-hospital cardiac arrest, local PICU discharge coding system for terms relating to cardiac arrest and out-of-hospital cardiac arrest, and existing cardiac arrest and acute life threatening events registries.

6.4.2 Study Design

Inclusion: Patients from 24 hours of age up to their 16th birthday, admitted to PICU after an OHCA with successful return of spontaneous circulation were included. OHCA was defined as no signs of cardiac output and pulseless for more than one minute as confirmed by a trained medical practitioner/paramedic prior to arrival at an emergency department.

Exclusion: Patients were excluded if they were younger than 24 hours of age or had a cardiac arrest secondary to birth asphyxia. This age limit was to exclude patients experiencing a perinatal event as standard treatment protocols regarding the use of therapeutic hypothermia are already established and this patient population is generally admitted to a neonatal unit and not to a PICU.

6.4.3 Data Collection and Assessment

Retrospective review of individual case notes, PICU nursing charts and computerised patient records was performed in each centre.

Data were recorded electronically onto a piloted Excel (Microsoft, USA) spreadsheet and saved on to a secure NHS Trust fire-wall protected computer server. Encrypted files were transferred to the chief investigator at Birmingham Children's Hospital via secure encrypted *nhs.net* email server accounts for central data management, data validation, and collation for formal statistical analysis. A data-entry guide and instruction booklet was created. One to one training was provided for data collectors in each institution by the chief investigator. Data were verified at the inputting stage using data-verification limits set in the excel programme which generated a warning message for values outside expected ranges. Individual queries were cleared directly by the chief investigator with regular reviewing of progress. Further data-verification was undertaken during the analysis stage with significant outliers, unexpected or improbable values and missing values queried and re-checked with the primary records by the relevant data-collector.

Data were collected using Utstein recommended definitions when available. Figure 6-1 shows the data collection domains and time points. Demographic data included; age, weight, sex, presence of chronic conditions prior to OHCA and requirement for transportation to PICU from another hospital. A chronic condition was defined as a pre-existing medical condition likely to increase risk of a cardiac arrest. Aetiology of arrest was extrapolated from medical documentation using information up to the time of discharge from PICU or from post-mortem reports if available. Categories included; pulmonary, cardiac, submersion (including near-drowning), neurological (non-traumatic), sepsis, inflicted traumatic brain injury, strangulation, (near) sudden infant death, trauma (including traumatic brain injury but excluding other injury related aetiologies already listed). Further comparative groupings of aetiology included asphyxial versus cardiac aetiology (cardiac group included patients with primary shockable rhythm or identified acute cardiac event) and non-traumatic versus traumatic aetiology (including all trauma aetiologies; submersion, hanging or strangulation, inflicted and non-inflicted traumatic brain, electrocution and 'other' trauma).

Cardiac arrest event characteristics were collected including place of arrest, whether it was a witnessed arrest, initiation of bystander cardiopulmonary resuscitation, first recorded rhythm on ECG monitor by paramedic or emergency medicine staff, use and number of cardiac

defibrillation attempts and number of doses of epinephrine. Date and time of important events were recorded as illustrated in Figure 6-1. Time intervals were calculated including duration of cardiac arrest (time of arrest to ROSC), duration of resuscitation after arrival in the emergency department arrival to ROSC, time from ROSC to PICU admission, and length of stay in PICU and hospital.

Physiological variables routinely available between ROSC and PICU admission were collected. Data were recorded whilst in the emergency department, during transportation and on arrival to PICU. Further data were collected at four hourly intervals after PICU admission. Maximum and minimum variables between ROSC and four hours post PICU admission were created. The use of data up to four hours post PICU arrival reduced the missing data for variables where blood gases were not being immediately sampled from patients and reflects the potential 'time window' of patient recruitment into a clinical trial. Additional physiological data was collected up to 24 hours post admission to allow comparison of the trend in variables and time to normalisation.

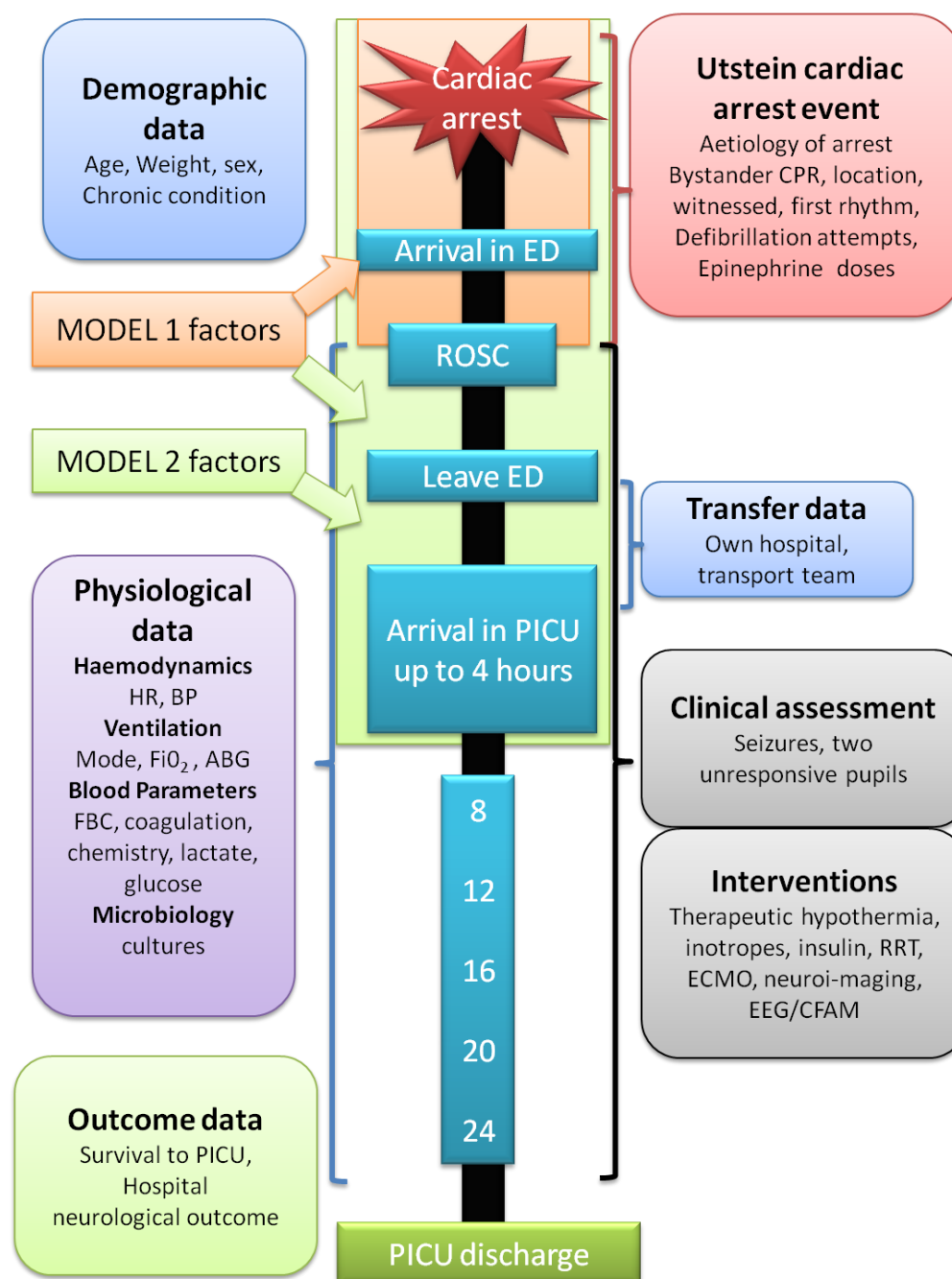
Core temperature was collected if recorded at additional time points; at the time of out-of-hospital cardiac arrest, return of spontaneous circulation, admission to ED, leaving ED, admission to PICU and every four hours from PICU admission (time zero) to 24 hours post admission. Core temperature was defined as either a rectal, oesophageal or bladder measurement. Episodes of severe hypothermia, defined as a core temperature less than 32°C, and hyperthermia, defined as a core temperature greater than 38°C, were recorded.

Occurrence of seizures within the period from ROSC to 24 hours, presence of two unresponsive pupils at PICU admission, and any major complication was also collected.

Post arrest treatments and investigations included; therapeutic hypothermia, use of mechanical ventilation, inotropic support, extracorporeal life support (ECLS), renal replacement therapy (including haemofiltration and peritoneal dialysis), insulin therapy, anti-seizure therapy, use and type of neuro-imaging and neuro-electrophysiological investigation. The use of therapeutic hypothermia was defined as documented active targeted temperature management to reduce or maintain core temperature to less than 35°C and greater than 32°C.

Primary outcome was survival to PICU discharge. Information on survival to hospital discharge and at one year was collected if available. Survival to PICU discharge was chosen owing to concerns about missing data in the hospital survival status. Unfortunately, a number of patients who survived to PICU discharge were discharged to another hospital and their survival status at hospital discharge could not be verified. We attempted to assess neurological outcome using information in the medical notes to allocate a patient a Paediatric Cerebral Performance Category (PCPC) score (Fiser et al, 2000) at PICU discharge and hospital discharge. Unfortunately the recording of information to enable category scoring was missing in up to 50% of survivors and therefore neurological outcome scoring could not be used in the analysis.

Figure 6-1 Study flow chart showing data collection areas at key time points.



Model 1: Factors available preceding cardiac arrest and during resuscitation for multivariable logistic regression model 1

Model 2: Inclusion of factors in model 1 and additional physiological and clinical factors available up to four hours after PICU admission for multivariable logistic regression model 2

HR: heart rate, BP: blood pressure (systolic and mean), Mode: conventional ventilation or high frequency oscillation, FiO₂: fractional inspired concentration of oxygen, ABG: arterial blood gas, FBC: full blood count, Chemistry: blood urea, creatinine, and magnesium levels. RRT: renal replacement therapy, ECMO: extracorporeal membrane oxygenation, EEG/CFAM: electroencephalography and cerebral function monitoring.

6.4.4 Statistical Analysis

We planned *a priori* two separate analyses of the data. This chapter reports on an analysis comparing survivors with non-survivors to evaluate predictive factors for the survival. A secondary analysis in the following chapter 7 will compare patients receiving therapeutic hypothermia with those who did not receive therapeutic hypothermia.

Data were tested for normality by using the Shapiro-Wilk's W test. Descriptive data are reported as median and interquartile range (IQR) for continuous variables and as frequencies and percentages for categorical variables. Parametric continuous data were analysed using the unpaired Student t-test and non-parametric continuous data with the Mann Whitney U test or Kruskal-Wallis as appropriate. Categorical data were analysed using the Chi² or Fisher's exact tests as appropriate. Linear-by-linear association was used for ordered categorical testing.

Logistic regression was used to identify variables that were independently associated with survival. Normality and linearity of continuous variables was assessed and appropriate transformation was used where necessary. Firstly, associations with outcome were identified by univariate logistic regression analysis. All variables with $p < 0.1$ for survival were included in a multivariate logistic regression analysis model. Forward stepwise selection was applied to this group of potential predictors to obtain the final model. The criteria for variable selection were a significance level to enter of 0.05 and a significance level to stay of 0.10.

Two logistic regression models were created (as illustrates on Figure 6-1). Model 1 included variables available before and during the cardiac arrest resuscitation: age, VF/VT (vs. PEA/asystole/bradycardia), defibrillation attempted, doses of epinephrine, duration of cardiac arrest (arrest to ROSC interval) and ROSC prior to ED admission. We decided *a priori* to use continuous variables (if available) in the primary logistic regression model. The use of dichotomised, continuous variables (splitting the population into two distinct groups) is relatively common in medical research; however, it can be associated with a loss of statistical power and residual confounding (Altman & Royston, 2006). In addition the use of sample data derived cut-off points has the potential to cause significant bias and therefore we chose to avoid this in the primary analysis. We did perform a separate *post hoc* analysis

using the dichotomised epinephrine dose (no epinephrine versus one or more epinephrine doses) and will report on the implications of this adjusted model.

Model 2 included variables available from ROSC up to four hours after PIC admission: VF/VT (vs. PEA/asystole/bradycardia), defibrillation attempted, duration of cardiac arrest (arrest to ROSC interval), ROSC prior to ED admission, PIM2 score on PICU admission, maximum and minimum lactate values, maximum base excess, maximum glucose, maximum and minimum pH, minimum and maximum temperature, pupillary reaction to light, inotrope use and insulin therapy for hyperglycaemia. Addition of the dichotomised epinephrine doses (no epinephrine versus one or more epinephrine doses) and lactate greater than or equal to 3 mmol/l (versus less than 3 mmol/l) were included in a secondary *post-hoc* analysis.

Adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated for each model. Predicted probabilities of survival were calculated based on the logistic regression coefficient model. Sensitivity, specificity, positive and negative predictive values were calculated. The c-statistic or area under the Receiver Operating Characteristic (ROC) curve for the predicted model is reported with the Hosmer Lemeshow goodness of fit assessment of the model (Hosmer et al, 1997; Hanley & McNeil, 1982). Missing data were not imputed; complete case selection was used when variables were missing.

The results of the multivariate analyses were compared with a decision tree model created using Classification and Regression Tree (CART) analysis software within IBM-SPSS statistical package, with survival to PICU discharge as the dependent variable. The potential advantages of CART are that the findings are simpler to understand and more applicable to clinicians as a bedside tool (Andrews et al, 2002; Forsyth et al, 2008). In these models, data available up to four hours post PICU admission were used to generate a decision tree that best predicted death in PICU. A random subset of 50% of cases was selected as a training sample for the development of the decision tree and then applied to the remaining 50% test sample. Only the test sample results are reported with corresponding sensitivity, specificity, positive and negative predicted values for predicting death in PICU.

A p value of <0.05 was considered statistically significant throughout. Data analysis was performed using both IBM-SPSS Statistics version 19.0 software (SPSS Inc, Chicago, USA) and Minitab 16 (USA).

All statistical analysis was performed by Dr Barney Scholefield (chief investigator and author) with advice from Dr Paul Davies (Statistical Advisory Service, Birmingham Children's Hospital Research & Development department).

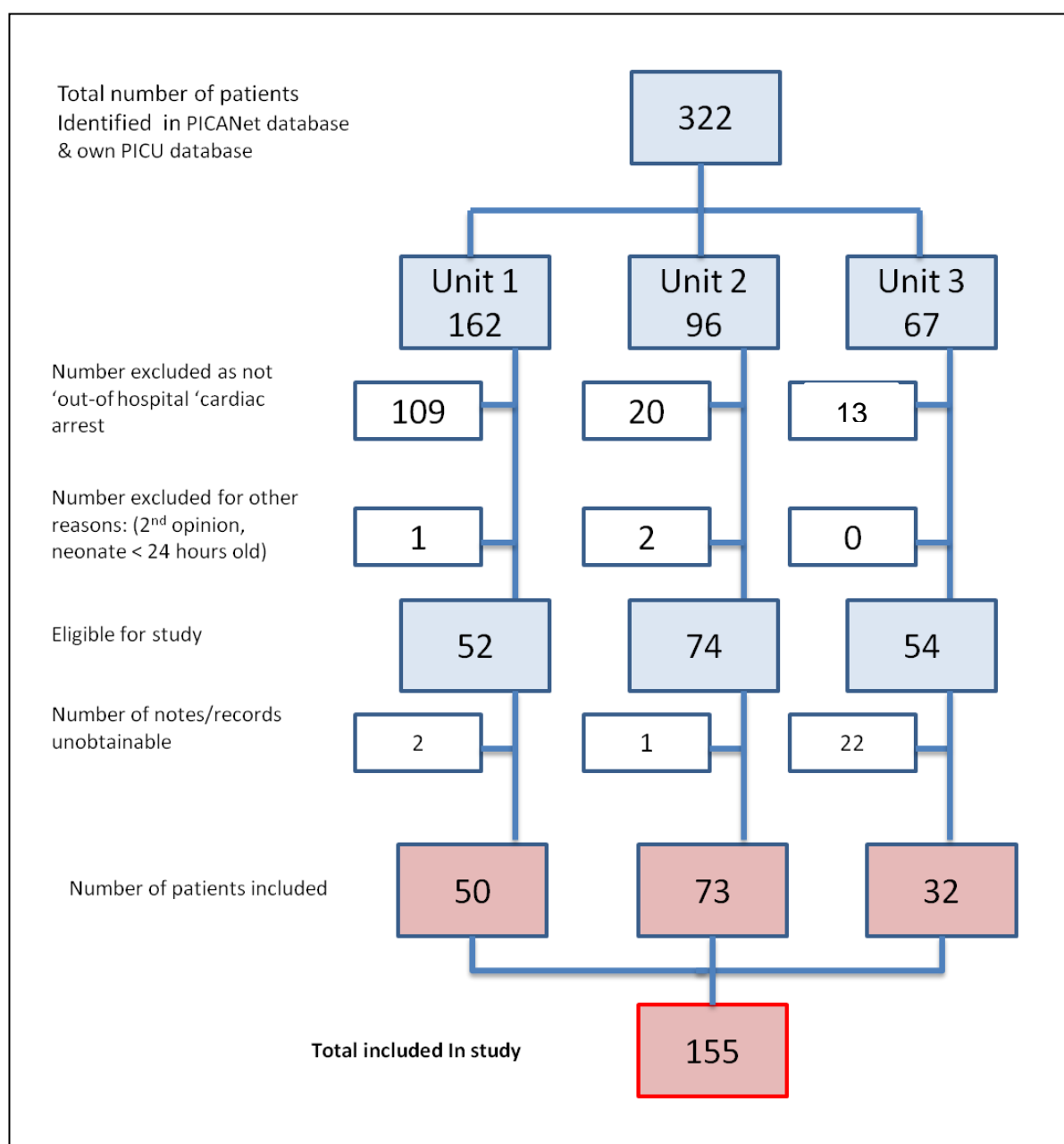
6.4.5 Ethics

Approval for this study was granted by the research and development department at Birmingham Children's Hospital (see letter of approval Appendix 9.11, p332). Regional ethics committee approval was not required as only medical data, routinely documented during hospital admission, were used. The collection of patient data was done by members of the patient's own health care team. Patient confidentiality and data protection was enforced by all three centres with the use of pseudo-anonymized data. Unique study identification numbers were created. Original linkage information of the study ID and patient record number was securely stored at each respective institution. Full compliance was maintained with local and national Good Clinical Practice guidelines and regulatory requirements.

6.5 RESULTS

322 patients were identified from database searches. After exclusion of 145 patients not fulfilling the inclusion criteria, 155/180 eligible patients were included from the three intensive care units. The remaining 25 (14%) of case notes were unobtainable, the majority from unit 3. Study inclusion flow chart is displayed in Figure 6-2.

Figure 6-2 Flow chart of included patients from individual units



6.5.1 Demographics

Table 5-3 describes baseline demographic and pre-existing chronic conditions for survivors and non-survivors after OHCA. Overall survival rate to PICU discharge was 32% (50/155). Median age of the total cohort was 1.3 yrs (IQR 0.2-5.5yrs). The majority, 45% (70/155), were less than one year of age (Figure 6-3). 62% were male with 42% having a pre-existing chronic condition. Neurological disorders were the commonest pre-existing chronic condition. There was no difference in age, sex and proportion with pre-existing chronic condition between survivors and non-survivors. Survival rates were constant across Utstein defined age groups (Figure 6-4). Unit one had the highest survival rate (42%) compared with unit two (30%) and unit three (22%), although Chi² statistical test was not significant ($p = 0.142$). 73% (111/150) of patients required transportation from a different hospital to the PICU and need for transportation was not associated with survival ($p = 0.336$). However, there was a significant difference in the need for transportation between Unit 1 (100%; 50/50), Unit 2 (51%; 37/71) and Unit 3 (78%; 25/32) ($p = 0.001$). The 111 patients transported to PICU were from 61 different emergency departments (Median 1 (IQR [1 to 2]) patient per emergency department).

Table 6-1 Demographics and relationship to PICU survival

	Total Group n=155	Survivors n=50	Non- survivors n=105	p ^b	missing
Age (years)	1.3 (0.2-5.5)	1.6 (0.2-9.1)	1.2 (0.3-5.3)	0.793	0
Weight (kg)^a	10 (4.7-20.3)	12 (4-25)	10 (5-20)	0.881	17
Age category (Utstein^b)				0.875	0
1-30 days	21 (14%)	9 (18%)	12 (12%)		
31 days to < 1yr	50 (32%)	15 (30%)	35 (33%)		
1yr to < 4yrs	39 (25%)	12 (24%)	27 (26%)		
4yrs to < 12yrs	20 (13%)	6 (12%)	14 (13%)		
12yrs to < 16yrs	25 (16%)	8 (16%)	17 (16%)		
Male	95 (62%)	34 (70%)	61 (59%)	0.202	0
Chronic Condition	65 (42%)	23 (46%)	42 (40%)	0.479	0
Two or more chronic conditions	23 (15%)	5 (10%)	18 (17%)	0.171	0
Neurological	24 (15%)	6 (12%)	18 (17%)	0.408	
Respiratory	18 (12%)	7 (14%)	11 (10%)	0.522	
Cardiac	15 (10%)	4 (8%)	11 (10%)	0.626	
Prematurity	8 (5%)	5 (10%)	3 (3%)	0.113	
Genetic	8 (5%)	1 (2%)	7 (7%)	0.220	
Metabolic	5 (3%)	2 (4%)	2 (3%)	0.707	
Gastrointestinal	2 (1%)	0	2 (2%)	ns	
Renal	2 (1%)	0	2 (2%)	ns	
Haematological	1 (1%)	0	1 (1%)	ns	
Admitting PICU				0.142	0
Unit 1	50	21 (42%) ^c	29 (58%)		
Unit 2	73	22 (30%) ^c	51 (70%)		
Unit 3	32	7 (22%) ^c	25 (78%)		
Transported from different admitting hospital	111 (73%)	38 (70%)	73 (78%)	0.336	2

^a Recorded weight (both estimated or measured) ^bUtstein pre-defined age groups with modified upper age limit to less than 16 years (Zaritsky et al, 1995). Unavailable (missing) values were excluded from calculations of summary statistics. Results expressed as Median (Inter-quartile range) or number (percent).

^b Chi² test was used for categorical variable and Mann Whitney U test for continuous variables.

^c Percent expressed as survivors per unit.

Figure 6-3 Chart of percent of survivors and non-survivors by age (years)

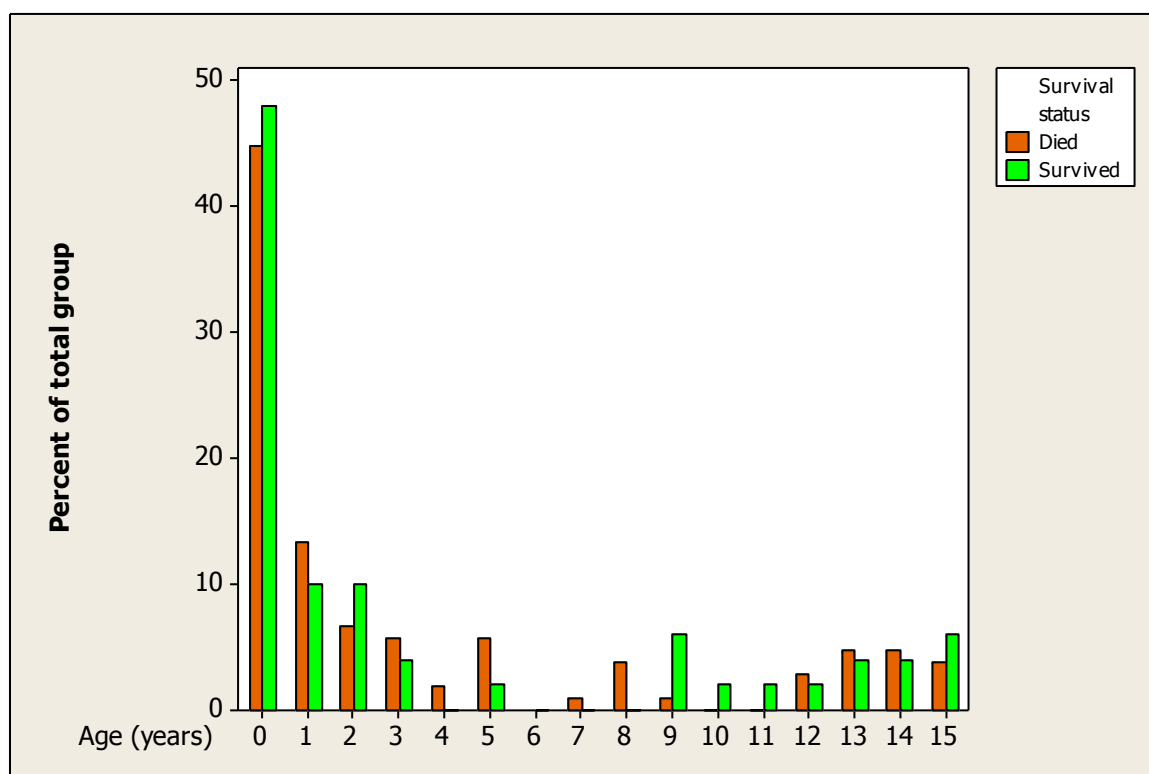
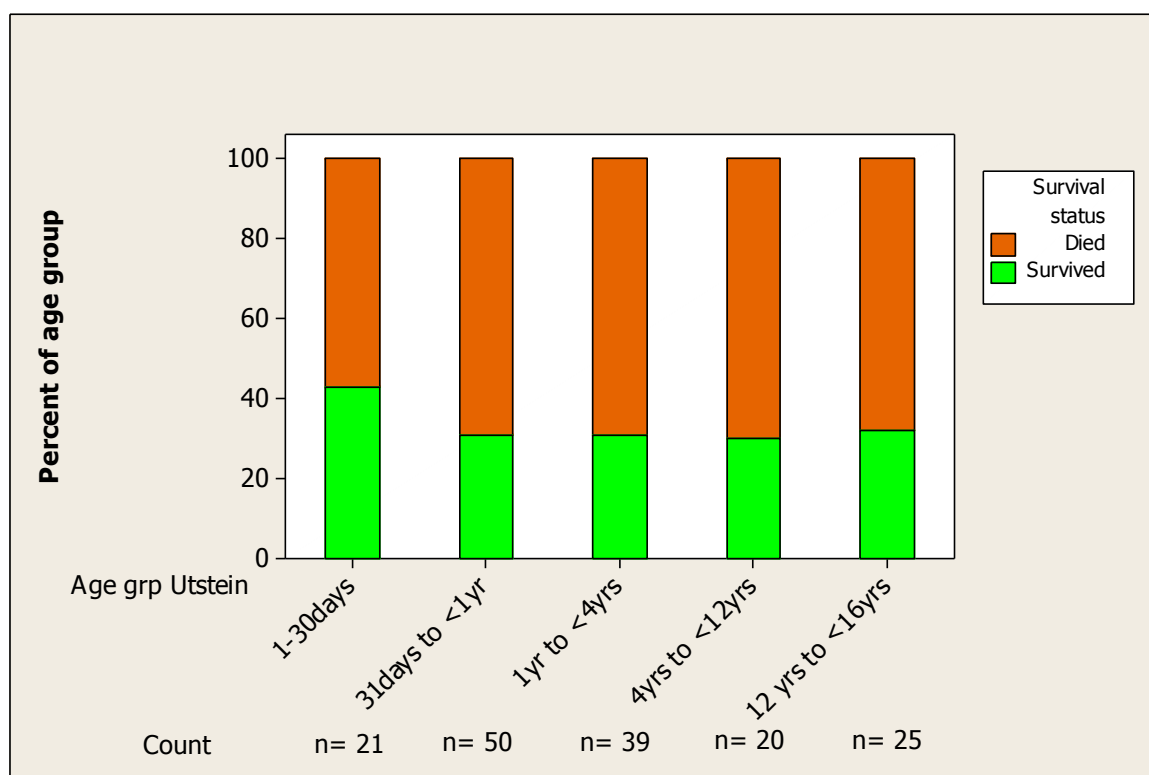


Figure 6-4 Chart of Utstein defined age groups for survivors and non-survivors



6.5.2 Aetiology

Table 6-2 describes the aetiology of OHCA. The aetiology was unknown in 18% (27/155) of patients. Pulmonary and cardiac aetiologies were the most common. There were no survivors after strangulation (0/9) and only 1/9 after inflicted traumatic brain injury. When analysing the overall groups, cardiac versus asphyxial (non-cardiac) aetiologies (Table 6-3) and traumatic versus non-traumatic aetiologies (Table 6-4), similar survival rates within each group were demonstrated.

Table 6-2 Aetiology of arrest and relationship to PICU survival

	Total Group n=155	Survivors n=50	Non- survivors n=105	p^b
Not Known	27 (18%)	7 (14%)	21 (20%)	
Pulmonary	28 (18%)	11 (22%)	17 (16%)	
Cardiac	18 (12%)	9 (18%)	9 (9%)	
Trauma (including accidental traumatic brain injury)	13 (8%)	5 (10%)	8 (8%)	
Submersion	12 (8%)	5 (10%)	7 (7%)	
Neurological	11 (7%)	3 (6%)	8 (7%)	
Sepsis	10 (6%)	3 (6%)	7 (7%)	
Inflicted traumatic brain injury	9 (6%)	1 (3%)	8 (8%)	
Strangulation	9 (6%)	0 (0)	9 (9%)	
Sudden infant death syndrome	7 (5%)	1 (2%)	6 (6%)	
Other	10 (6%)	5 (10%)	5 (5%)	0.204

Unavailable (missing) values were excluded from calculations of summary statistics. Results expressed as Median (Inter-quartile range) or number (percent).

^b Chi² test was used for overall trend analysis of categorical variable

Table 6-3 Asphyxia versus cardiac aetiology and relationship to PICU survival

	Total Group	Survivors	Non-survivors	p^b	missing
Asphyxial	109	34 (31%)	75 (69%)	0.118	28
Cardiac	18	9 (50%)	9 (50%)		

Unavailable (missing) values were excluded from calculations of summary statistics. Results expressed as number (percent).

^b Chi² test. Percentages calculated across asphyxial and cardiac group

Table 6-4 Traumatic versus non-traumatic aetiology and relationship to PICU survival

	Total Group	Survivors	Non-survivors	p^b	missing
Traumatic^c	45	13 (29%)	32 (71%)	0.381	28
Non-Traumatic	82	30 (37%)	52 (63%)		

Unavailable (missing) values were excluded from calculations of summary statistics. Results expressed as number (percent).

^b Chi² test Percentages calculated traumatic and non-traumatic groups

^cTrauma aetiology included inflicted and accidental traumatic brain injury, submersion, strangulation, electrocution and 'other' trauma.

6.5.3 Cardiac arrest event factors

Table 6-5 describes the cardiac arrest event factors and relationship to survival. Arresting in the home, having a witnessed arrest or receiving bystander cardiopulmonary resuscitation was not significantly associated with survival. Survivors were more likely to present in a shockable rhythm (VF or pulseless VT) ($p = 0.001$) and receive cardiac defibrillation ($p = 0.02$) whereas non-survivors were more likely to be asystolic (53% vs. 21%). Non-survivors received more doses of adrenaline than survivors ($p = 0.01$). Figure 6-5 illustrates the significant reduction in survival in patients receiving one or more doses of adrenaline versus none ($p = <0.001$); however, unadjusted survival rates remain constant with one or increasing doses of adrenaline.

Table 6-5 Cardiac arrest resuscitation events and relationship with PICU survival

Cardiac arrest resuscitation events	Total Group N=155	Survivors n=50	Non-survivors = 105	<i>p</i> ^b	missing
Location own home (versus public place or other)	104 (71%)	33 (72%)	71 (71%)	0.927	9
Witnessed arrest	96 (63%)	34 (72%)	61 (59%)	0.122	
Bystander CPR	98 (66%)	33 (72%)	65 (64%)	0.34	6
VF/VT^a (vs. PEA/bradycardia/asystole)	17 (12%)	11 (29%)	6 (6%)	<0.001	16
Pulseless electrical activity (PEA)	17 (12%)	6 (15%)	11 (11%)		
Bradycardia	44 (32%)	14 (36%)	30 (30%)		
Asystole	61 (44%)	8 (21%)	53 (53%)		
Ventricular fibrillation (VF)	7 (5%)	4 (10%)	3 (3%)		
Pulseless Ventricular tachycardia (VT)	10 (7%)	7 (18%)	3 (3%)		
Defibrillation attempted	26 (17%)	13 (28%)	13 (13%)	0.022	12
Epinephrine doses during resuscitation. Median (IQR)	3 (1-4)	2 (0-4)	3 (2-4)	0.01	4
No epinephrine given during resuscitation	18 (12%)	14 (29%)	4 (4%)	<0.001	4

Values expressed as: Numbers (percent of total group, survivors or non-survivors) unless stated. CPR denotes cardiopulmonary resuscitation. ^aFirst recorded rhythm after cardiac arrest. VF: ventricular fibrillation, VT: ventricular tachycardia, PEA: pulseless electrical activity

^aUnavailable (missing) values were excluded from calculations of summary statistics. Results expressed as Median (Inter-quartile range) or number (percent).

^b Chi² test was used for categorical variable and Mann Whitney U test for continuous variables.

Figure 6-5 Number of doses of epinephrine and survival status



* excludes 4 missing values

6.5.4 Time factors

Table 6-6 describes the time interval data in relation to resuscitation and PICU admission. Survivors had shorter duration of time from cardiac arrest onset to return of spontaneous circulation (ROSC) ($p=0.002$) and a larger proportion (23 vs. 10%) achieved ROSC prior to ED admission ($p=0.049$). Duration of CPR in the hospital emergency department for those not achieving ROSC before admission was similar for survivors and non-survivors.

Figure 6-6 illustrates decreasing survival rates for longer duration of cardiac arrest, although, 1 in 4 patients with 30 minutes or more resuscitation survived.

Figure 6-7 illustrates a similar trend of worsening survival for increasing duration of continued CPR after arrival to hospital. 21% (3/14) patients receiving CPR for 21 to 30 minutes in the emergency department, survived. 35% (7/20) survived with more than 30 minutes of CPR in hospital. Of the survivors in this group; 0/7 had chronic conditions, 2/7 arrested secondary to submersion and 5/7 received bystander CPR. Overall 86% of patients in the study had continuing CPR at the time of hospital arrival; (however, this occurred in more non-survivors (90 vs. 77%; $p=0.046$).

Time from ROSC to admission to PICU for the whole group was similar for survivor and non-survivors (4hrs 45mins vs. 4hrs 15mins; $p = 0.177$). Length of stay in PICU was significantly longer for survivors than non-survivors. Figure 6-8 illustrates the left skewed distribution of time to death or discharge of non-survivors versus survivors. 26% (27/105) of non-survivors died within 24 hours of ROSC.

Table 6-6 Time data

	Total Group N=155	Survivors n=50	Non- survivors = 105	<i>p</i> ^b	missing
Time from cardiac arrest to ROSC (mins)	35 (20-50)	22 (11-45)	39 (25-55)	0.002	19
ROSC prior to ED admission	20 (14%)	10 (23%)	10 (10%)	0.046	16
Time from ED admission to ROSC (mins) ^a	15 (7-25)	11 (4-28)	15 (8-25)	0.173	16
Time from ROSC to PICU admission (hrs:mins)	4:22 (2:22-5:37)	4:45 (2:25-5:53)	4:15 (2:10-5:09)	0.177	16
Length of stay in PICU (days)	3.0 (1.3-6.2)	6.2 (2.8-8.1)	2.3 (0.9-4.5)	<0.001	3

ROSC denotes return of spontaneous circulation. ED: emergency department, PICU Paediatric intensive care unit. Unavailable (missing) values were excluded from calculations of summary statistics. Results expressed as Median (Inter-quartile range) or number (percent of total group, survivors or non-survivors).

^a Only patients receiving CPR at ED admission were included in calculation

^b Chi² test was used for categorical variable and Mann Whitney U test for continuous variables.

Figure 6-6 Survival rates for increasing duration of cardiac arrest time

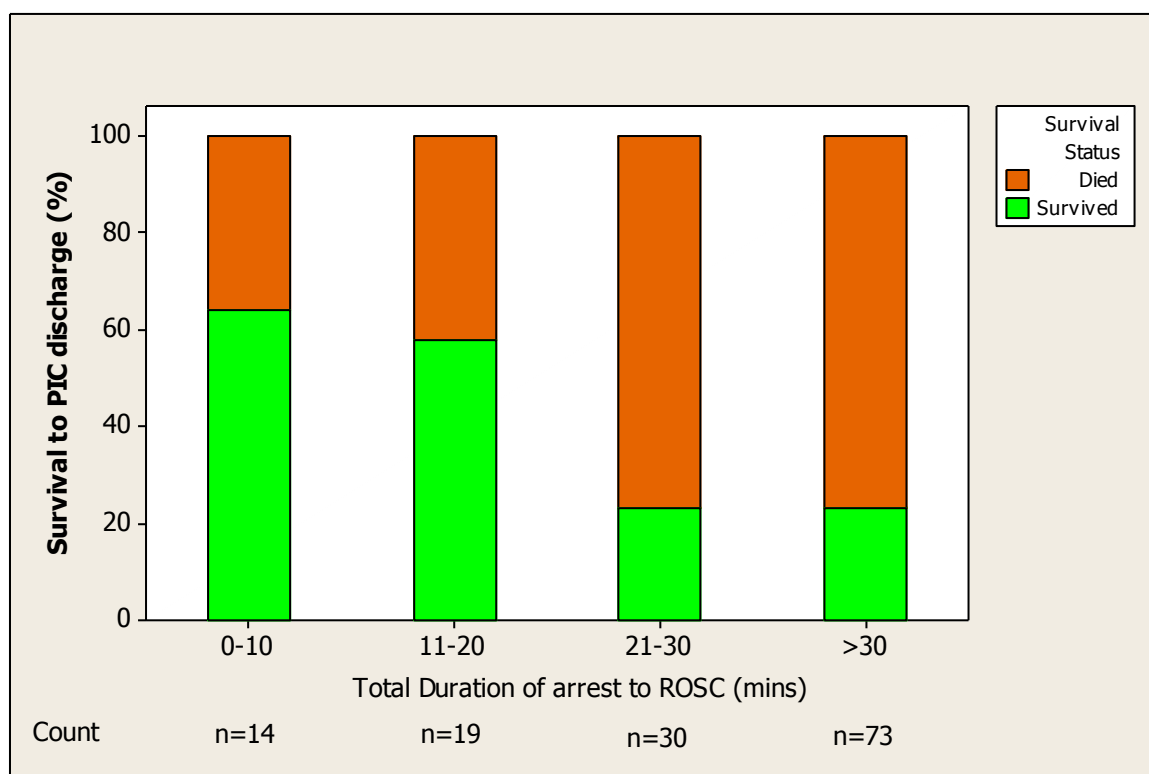


Figure 6-7 Survival rates for duration of resuscitation time in the ED

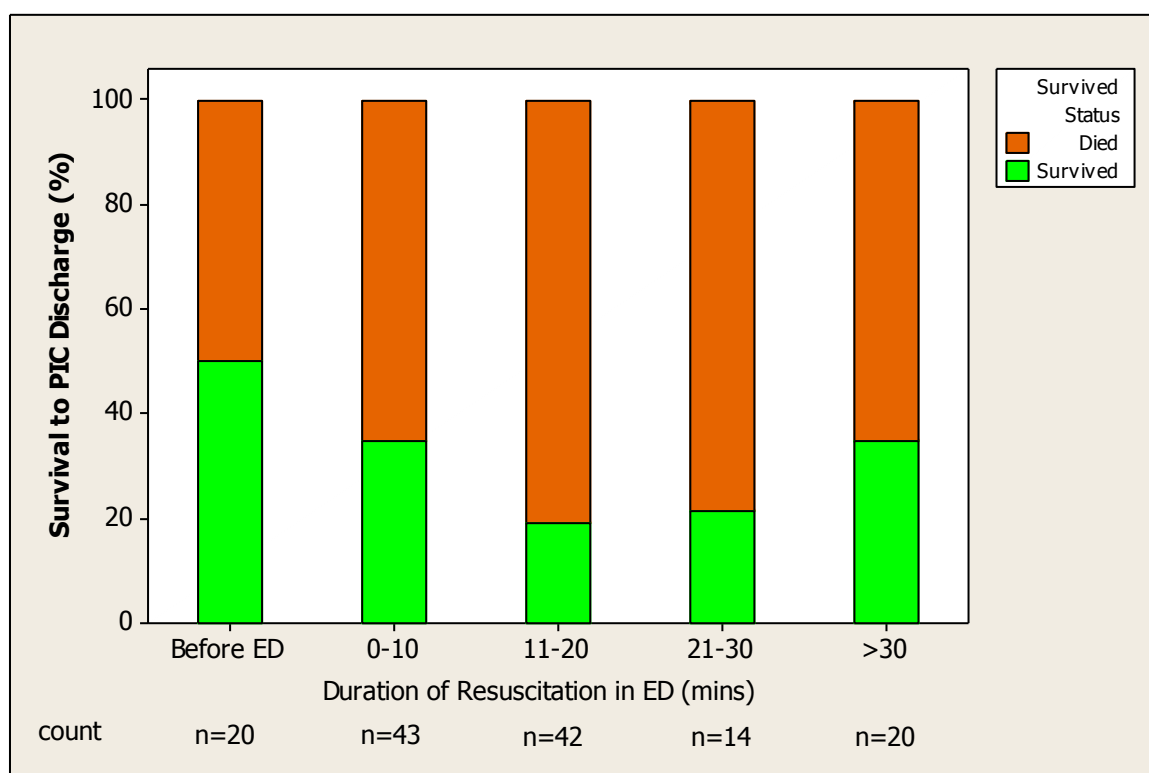
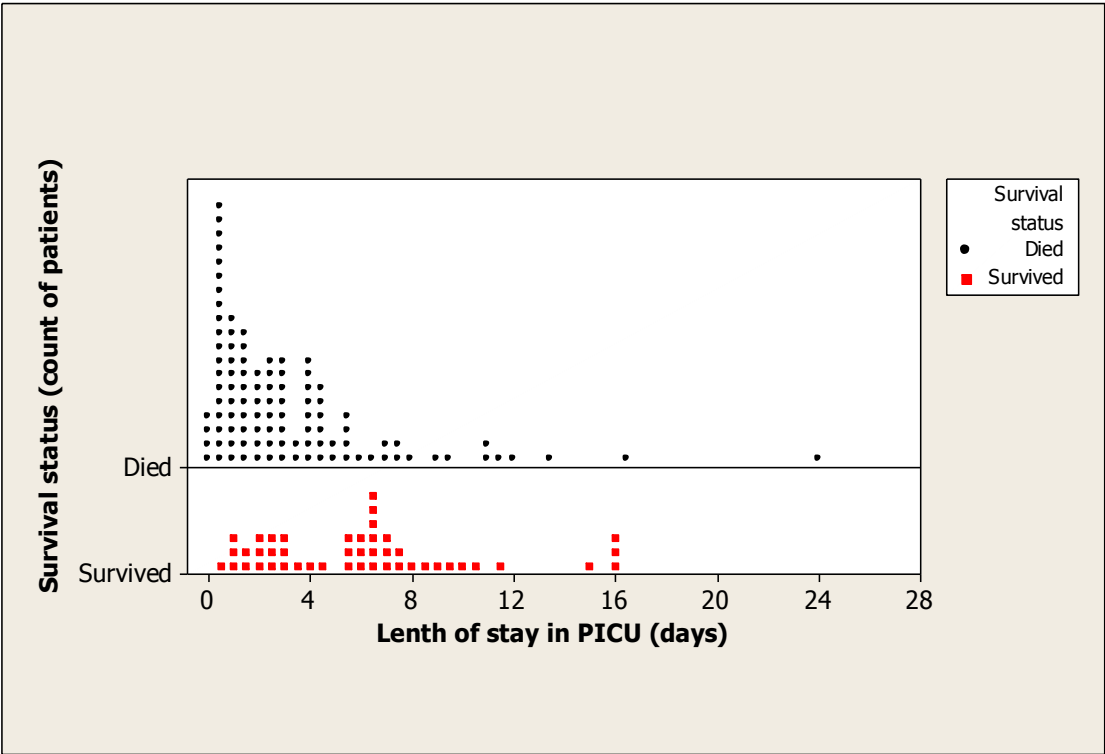


Figure 6-8 Dot plot of length of stay in PICU for survivors and non-survivors



Each dot represents an individual patient. Excludes one outlier who survived to PICU discharge after 361 days

6.5.5 Physiological and clinical variables after ROSC

Table 6-7 describes physiological variables available between ROSC and four hours after PICU admission. Survivors had significantly less physiological derangement on all reported variables compared to non-survivors. This included; higher pH, lower lactate, lower glucose and higher base excess. PIM2 score, which included pH, base excess, PaO₂/FiO₂ ratio, pupillary reaction status and additional medical history details, but did not include lactate, was significantly lower for survivors. Survivors were more likely to have two responsive pupils. However the rates of documented seizures were not statistically different (Table 6-8).

Using physiological variables up to four hours after PICU admission, compared to only at PICU admission, reduced the number of missing values from 17% (27/155) to 12% (16/155) for lactate levels and from 13% (20/155) to 6% (9/155) for pH and glucose results.

Figures 6-9, 6-10, 6-11 and 6-12 show the comparative trend in physiological variables for survivors and non-survivors from arrival to the emergency department, PICU admission and every four hours up to 24 hours post PICU admission.

In the emergency department pH and base excess were significantly different between survivors and non-survivors; however, there was a large number of missing values. On PICU admission pH, lactate, glucose and base excess were all significantly different between survivors and non-survivors. There was no significant difference noted after 8 hours for pH, after 12 hours for glucose and after 16 hours for lactate. Base excess remained significantly different between survivors and non-survivors until 24 hours after PICU admission.

Table 6-7 Physiological and laboratory variables (between ROSC to four hours after PICU admission) and relationship to PICU survival

	Total Group N=155	Survivors n=50	Non- survivors = 105	p^b	missing
Minimum pH	6.90 (6.70-7.13)	6.95 (6.80-7.23)	6.80 (6.65-7.12)	0.015	9
Maximum pH	7.34 (7.24-7.42)	7.37 (7.35-7.43)	7.28 (7.21-7.4)	0.003	9
Minimum lactate (mmol/l)	3.6 (2.2-8.0)	2.3 (1.4-3.9)	5.3 (2.8-9.0)	<0.001	16
Maximum lactate (mmol/l)	9.0 (4.7-13.9)	5.78 (2.6-12.1)	9.3 (5.8-14.8)	0.009	16
Minimum glucose (mmol/l)	5.7 (3.9-9.6)	4.5 (3.6-7.0)	6.5 (4.3-10.9)	0.003	10
Maximum glucose (mmol/l)	15.8 (12.3-19.6)	13.8 (9.2-17.3)	16.7 (12.8-20.0)	0.018	10
Minimum base excess (mEq/L)	-18.5 (-24 to -12.4)	-14.0 (-21.0 to -8.5)	-20.1 (-25.1 to -13.9)	0.001	7
Probability of death by PIM2^a	0.84 (0.35-0.96)	0.39 (0.26-0.75)	0.92 (0.58-0.96)	<0.001	0
Lactate > 3 on PIC admission*	89 (69%)	18 (43%)	71 (83%)	<0.001	27

^a PIM2 (Paediatric index of mortality 2) (Slater et al, 2003) calculated on PICU admission data for all cases including patients transported by PICU specialist retrieval team

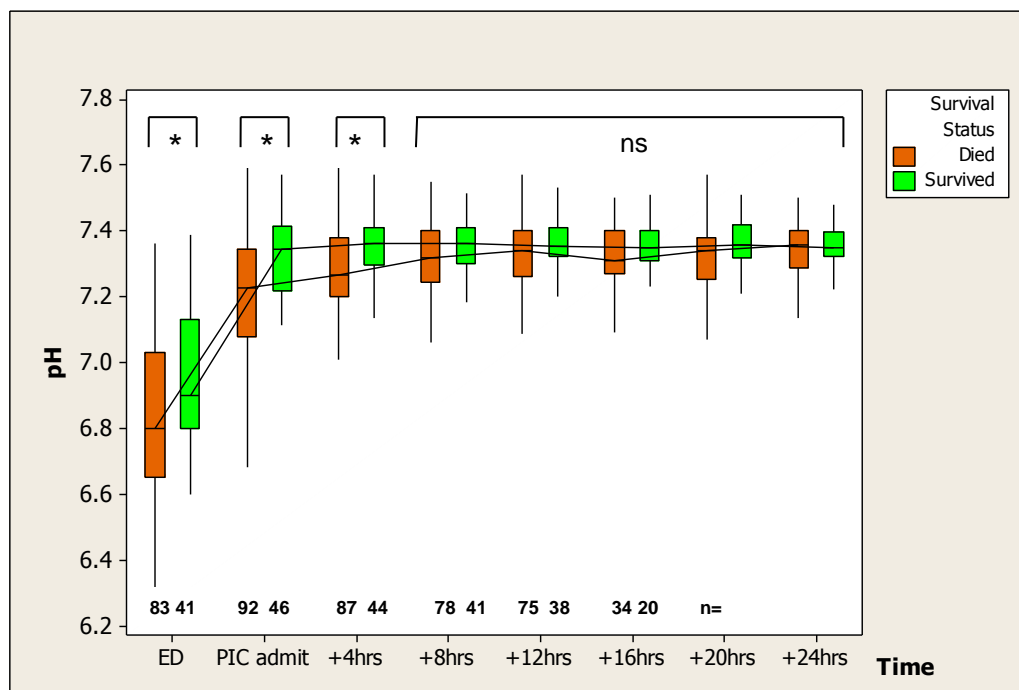
^b Unavailable (missing) values were excluded from calculations of summary statistics. Chi² test was used for categorical variable and Mann Whitney U test for continuous variables. Results expressed as Median (Inter-quartile range) or number (percent).

Table 6-8 Clinical neurological variables and relationship to PICU survival

	Total Group N=155	Survivors n=50	Non- survivors = 105	p^b	missing
Seizures	48 (31%)	12 (24%)	36 (34%)	0.222	6
Two unresponsive pupils	87 (66%)	12 (32%)	75 (80%)	<0.001	23

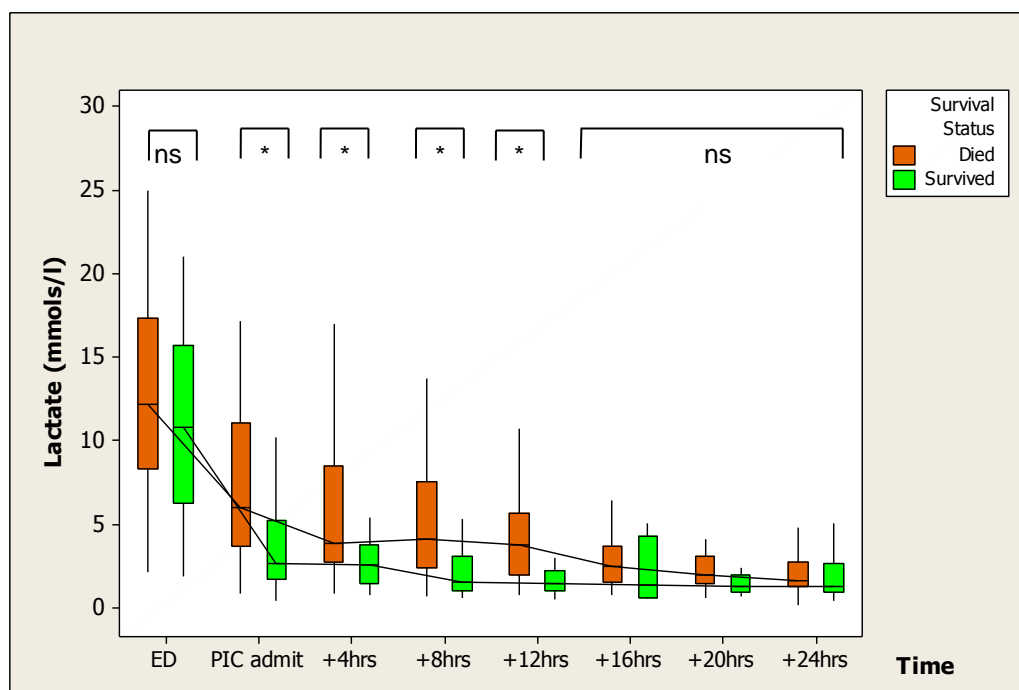
Results expressed as number (percent). ^b Unavailable (missing) values were excluded from calculations of summary statistics. Chi² test was used for categorical variable

Figure 6-9 Boxplot of pH for survivors and non-survivors from ED admission to 24 hrs post PIC admission



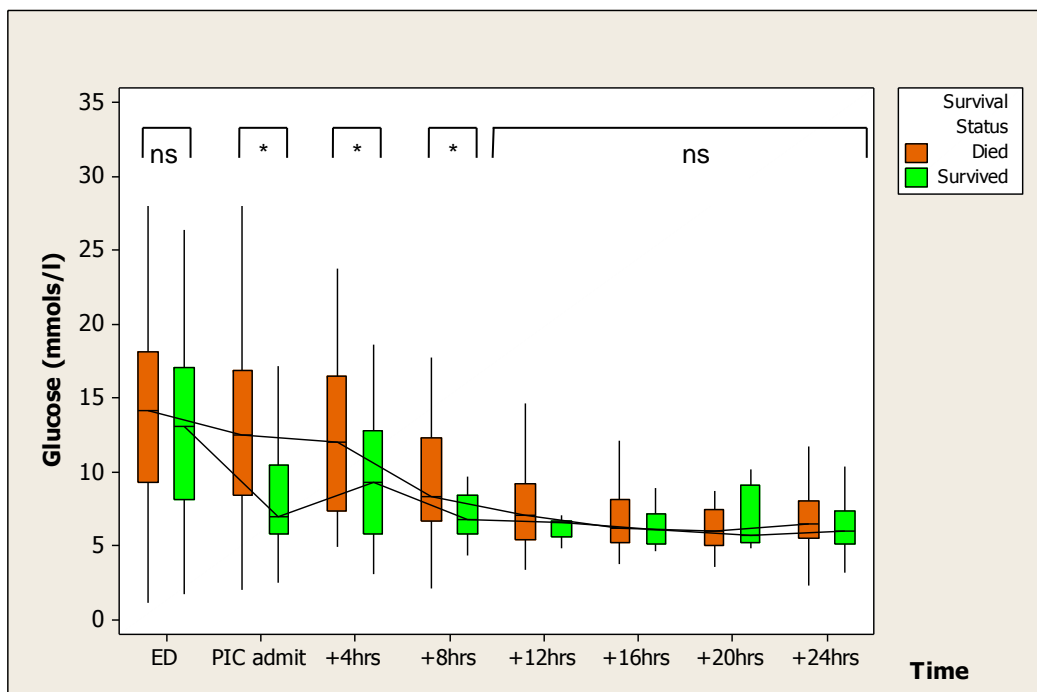
* $p < 0.05$ survivors versus non-survivors, ns = not significant ($p \geq 0.05$)

Figure 6-10 Boxplot of lactate for survivors and non-survivors from ED admission to 24 hrs post PIC admission



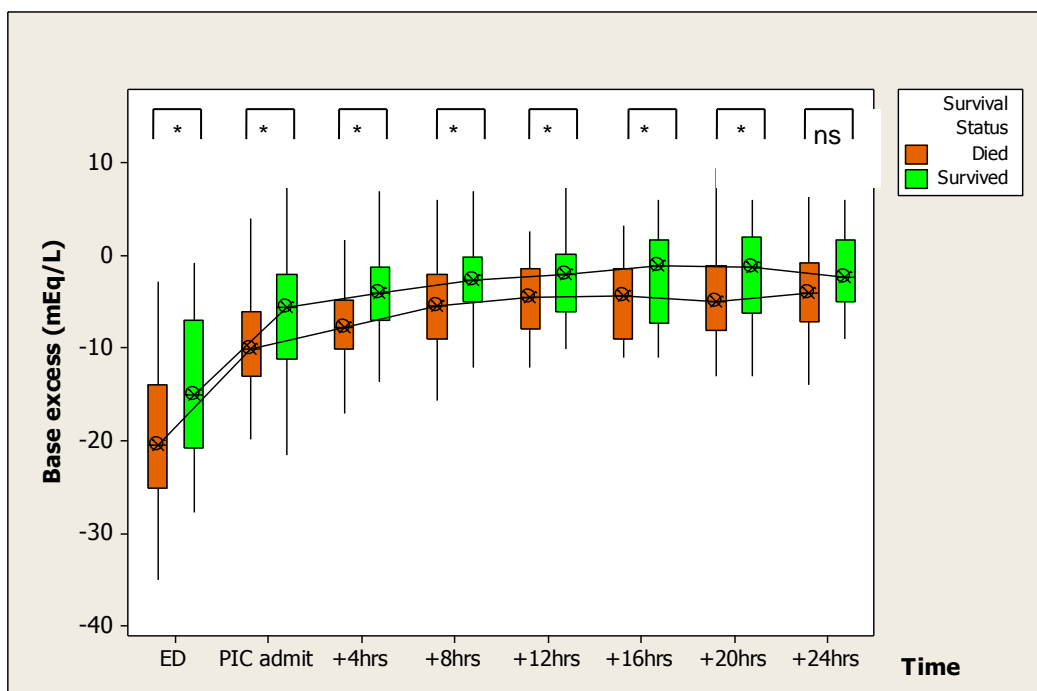
* $p < 0.05$ survivors versus non-survivors, ns = not significant ($p \geq 0.05$)

Figure 6-11 Box plot of glucose for survivors and non-survivors from ED admission to 24 hrs post PIC admission



* $p < 0.05$ survivors versus non-survivors, ns = not significant ($p \geq 0.05$)

Figure 6-12 Box plot of base excess for survivors and non survivors from ED admission to 24 hours post PIC admission



* $p < 0.05$ survivors versus non-survivors, ns = not significant ($p \geq 0.05$)

6.5.6 Temperature variability after ROSC

Table 6-10 describes the core temperature differences between survivors and non-survivors during different stages of post-ROSC management. An equal proportion of survivors (33%; 16/50) and non-survivors (30%; 32/105) received therapeutic hypothermia when admitted to PICU. Temperature measurements were available for 77% (115/155) patients in the period prior to PICU admission, although measured at varying time points. There was no difference in maximum or minimum median temperature between survivors and non-survivors in the emergency department; however, survivors appeared to have a higher median core temperature prior to leaving the emergency department.

On admission to PICU, non-survivors had a median core body temperature 1.0°C lower than survivors ($p=0.007$) (Table 6-10). Minimum temperature between ROSC and four hours post PICU admission was also significantly lower in non-survivors. However, maximum temperature was similar. Table 6-11 describes the association of hypothermia or hyperthermia with survival. Experiencing a core temperature less than 32°C after OHCA post ROSC and within 24 hours of PICU admission was associated with increased mortality ($p=0.017$); however, an episode of hyperthermia (temperature >38°C) was not associated.

Figure 6-13 illustrates the relationship of maximum and minimum temperature in the emergency department and temperature for 24 hours after PICU admission. Except for arrival at PICU, temperature of survivors and non-survivors was similar.

Table 6-9 Core temperature measurement in the emergency department (ED) and relationship to survival

	Total Group n=155	Survivors n=50	Non- survivors n=105	P	Missing value
Core temperature readings (°C)					
Temperature at arrival to ED	34.3 (32.3-35.3)	34.3 (33.0-35.5)	34.4 (32-35.5)	0.841	91
Temperature at ROSC	34.1 (32.5-35.2)	34.1 (34.0-35.4)	34.1 (32.5-35.1)	0.776	90
Temperature leaving ED	35.4 (34-36.5)	35.9 (34.9-36.5)	34.7 (33.2-36.3)	0.051	76
Minimum temperature recorded in ED	34.3 (32.4-35.5)	34.8 (34.0-35.6)	34.1 (32.0-35.5)	0.164	39
Maximum temperature recorded in ED	35.4 (34.3-36.2)	35.3 (34.8-36.3)	35.3 (34.1-36.2)	0.411	39

Values expressed as: Median (Interquartile range). Mann Whitney U test was used for continuous variables.

Table 6-10 Core temperature measurements at PICU admission and relationship to survival

	Total Group n=155	Survivors n=50	Non- survivors n=105	P	Missing value
Core temperature readings (°C)					
Temperature at PICU admission	35.8 (34.0-37.0)	36.5 (35.6-37.2)	35.5 (33.4-37.0)	0.007	19
Minimum temperature after ROSC To 4hrs post PICU admission	34 (32.2.-35.5)	34.5 (33.3-36.9)	33.3 (32-35.1)	0.011	6
Maximum temperature after ROSC To 4hrs post PICU admission	36.5 (35.5-37.5)	36.7 (36.0-37.5)	36.3 (35.2-37.5)	0.150	6

Values expressed as: Median (Interquartile range). Mann Whitney U test was used for continuous variables.

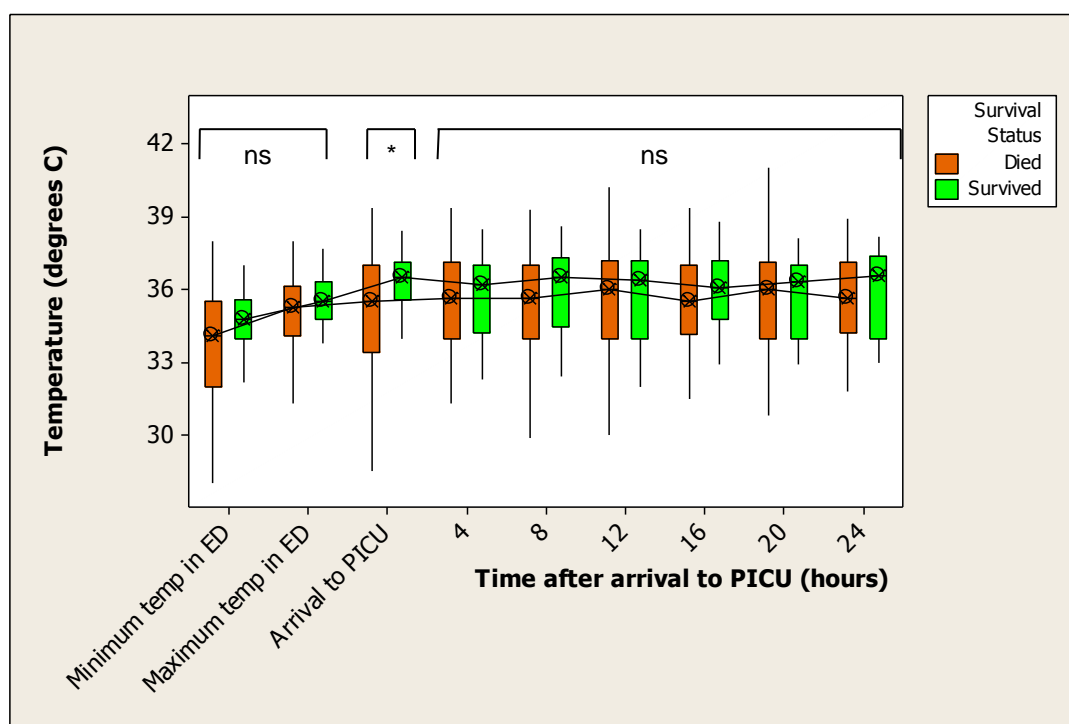
Table 6-11 Relationship between hypothermia or hyperthermia with survival

	Total Group n=155	Survivors n=50	Non-survivors n=105	P	Missing value
Any temperature <32°C ROSC to 24hrs post PICU admission	33 (22%)	5 (10%)	28 (28%)	0.017^a	6
Any temperature >38°C ROSC to 24hrs post PICU admission	45 (29%)	50 (32%)	33 (31%)	0.341 ^b	6

Unavailable (missing) values were excluded from calculations of summary statistics.

^aFishers Exact test and ^bChi² test were used for categorical variable

Figure 6-13 Box plot of core temperatures for minimum and maximum ED to 24 hours post PICU admission



* p<0.05 survivors versus non-survivors, ns = not significant (p ≥ 0.05)

6.5.7 Post cardiac arrest intensive care treatment and investigation

Table 6-12 describes the treatment and investigations received after resuscitation for survivors and non-survivors. 1 in 3 patients received therapeutic hypothermia; however, there was significant difference between Unit 1 (6%; 3/50), Unit 2 (52%; 38/73) and Unit 3 (22%; 7/32) ($p = 0.001$). All but one patient required mechanical ventilation. Inotrope use after ROSC was associated with increased mortality; however the combination of more than one type of inotrope was not associated with a change in outcome. Extra-corporeal life support (ECLS) and renal replacement therapy was rarely used in OHCA patients, although 10% received high frequency oscillation ventilation (HFOV). The use of insulin therapy was higher in the non-survivors but did not reach statistical significance owing to small sample size and half of patients had continued neuromuscular blockade after PICU admission.

The use of neuro-radiological imaging and neuro-electrophysiological monitoring was similar in survivors and non-survivors. 71% (109/155) received neuro-imaging and 43% (53/155) neuro- electrophysiological investigation.

Table 6-12 Post arrest treatment & Investigational data in relationship to PICU survival

	Total Group N=155	Survivors n=50	Non- survivors = 105	<i>p</i> ^b
Treatment				
Therapeutic hypothermia	48 (31%)	16 (33%)	32 (30%)	0.848
Mechanical ventilation	154 (99%)	49 (98%)	105 (100%)	0.323
Inotropes after resuscitation	99 (63%)	26 (53%)	73 (70%)	0.047
Two or more inotropes	43 (27%)	14 (29%)	29 (28%)	0.902
HFOV	15 (10%)	4 (8%)	11 (10%)	0.652
ECMO	3 (2%)	1 (2%)	2 (2%)	1.0
Renal replacement therapy	0	0	0	1.0
Insulin therapy	35 (23%)	7 (14%)	28 (27%)	0.088
Neuromuscular blockade after PICU admission	78 (50%)	23 (47%)	55 (53%)	0.529
Anti-seizure therapy	48 (31%)	12 (24%)	36 (34%)	0.222
Investigation				
Any neuroradiology	109 (71%)	33 (66%)	76 (73%)	0.366
MRI scan	37 (24%)	16 (32%)	21 (20%)	0.101
CT scan	88 (57%)	25 (50%)	63 (60%)	0.240
Any neuro-electrophysiology investigation ^c	53 (43%)	22 (51%)	31 (39%)	0.185

^bChi² test was used for categorical variable and Mann Whitney U test for continuous variables.

^cIncludes: Electroencephalogram (EEG) and continuous amplitude integrated EEG
MRI: magnetic resonance imaging, CT: Computer tomography

6.5.8 Model one: Univariate and multivariate logistic regression analysis

Table 6-13 shows the univariate analysis for model one including candidate variables available either prior to the cardiac arrest or during resuscitation. Variables with $p < 0.1$ were included in the multivariate logistic regression analysis. These included; presenting in a shockable rhythm (VF/VT vs. PEA/asystole/bradycardia), defibrillation versus no defibrillation, total duration of cardiac arrest (mins) and ROSC prior to ED admission versus continued CPR. Presenting in either VF or VT (odds ratio 8.3; $p = 0.001$) was strongly associated with increased survival. Model one predicted death in PICU with a sensitivity of 95% and specificity of 29% (positive predictive and negative predictive value of 77% and 71% respectively).

In a *post-hoc* analysis, inclusion of the epinephrine dose variable by dichotomising to no epinephrine versus one or more doses improved the fit of model one. Table 6-15 shows results of model one with *post hoc* adjustment. No epinephrine doses (odds ratio 11.98; $p = 0.003$) and presenting in either VF or VT (odds ratio 3.95; $p = 0.057$) were both strongly associated with increased survival. Figure 6-14 illustrates the Receiver Operator Characteristic (ROC) curve for model one with an Area Under the Curve (AUC or c-statistic) of 0.669. Hosmer Lemeshow goodness of fit test statistic was 0.386, indicating the logistic model is an acceptable fit. The *post-hoc* model one predicted death in PICU with a sensitivity of 94% and specificity of 43% (positive predictive and negative predictive value of 80% and 75% respectively).

Table 6-13 Model 1: Univariate logistic regression. Analysis of factors associated with PICU survival available before or during cardiac arrest

Variable	Unadjusted Odds Ratio for survival	95% CI	P value	missing
Age (yrs)	1.00	1.0-1.0	0.820	1
Sex (male)	0.67	0.33-1.36	0.265	0
Chronic condition (vs. no chronic condition)	1.28	0.65-2.52	0.480	0
Cardiac (vs. asphyxial) aetiology	2.21	0.8-6.05	0.124	28
VF/VT (vs. PEA/asystole/bradycardia)	6.15	2.09-18.13	0.001	16
Defibrillation vs. no defibrillation	2.60	1.1-6.16	0.030	3
Epinephrine doses (increment of 1)	0.90	0.77-1.05	0.174	4
Time duration from cardiac arrest to ROSC (mins)	0.98	0.96-1.0	0.021	19
ROSC prior to ED admission	2.61	0.99-6.83	0.051	16
Minimum temperature (°C) in ED	1.10	0.95-1.27	0.219	39
<i>Post hoc addition</i>				
No epinephrine (vs. one or more doses of epinephrine during resuscitation)	10.2	3.1-33.1	<0.001	4

VF: ventricular fibrillation, VT: ventricular tachycardia, PEA: pulseless electrical activity, ED emergency department, ROSC: return of spontaneous circulation. 95% confidence interval (CI).

Table 6-14 Model 1: Multivariate logistic regression analysis of factors associated with PICU survival before or during cardiac arrest

Variable	Odds ratio for survival (n=122)	95% CI	P value
VF/VT (vs. PEA/asystole/bradycardia)	8.3	2.4-28.7	0.001

c-statistic: 0.611

Sens = 95%, Spec= 29%, PPV = 77%, NPV = 71%

Factors entered into model: VF/VT (vs. PEA/asystole/bradycardia), defibrillation attempt, ROSC prior to ED admission versus continued CPR on admission and duration of cardiac arrest (arrest to ROSC). Total cases in model = 122.

Sensitivity (Sens), Specificity (Spec), Positive Predicted Value (PPV), Negative Predicted Value (NPV).

Table 6-15 Model 1 (post-hoc adjustment): Multivariate logistic regression analysis of factors associated with PICU survival before or during cardiac arrest with inclusion of dichotomised epinephrine dose category.

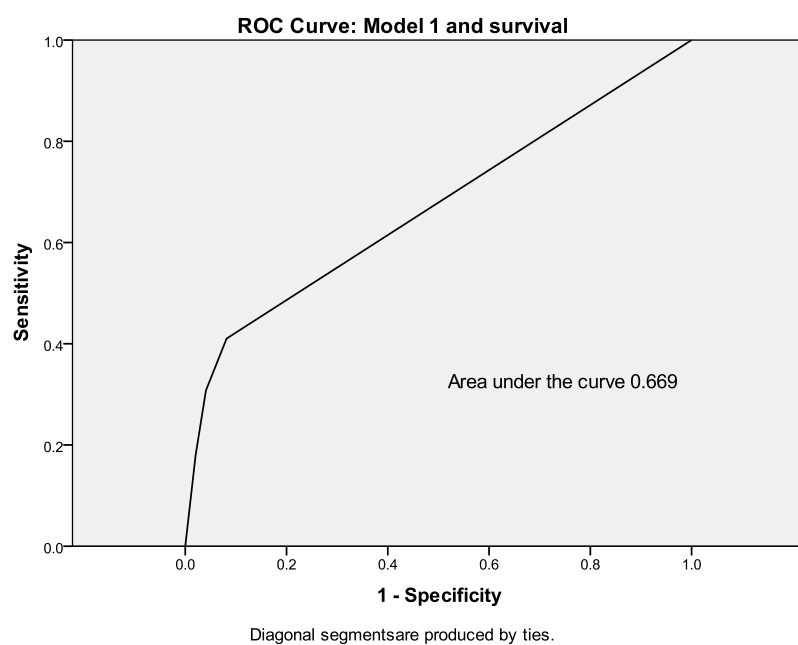
Variable	Odds Ratio for survival (n=122)	95% CI	P value
No epinephrine (vs. one or more doses of epinephrine during resuscitation)	11.98	2.31-61.99	0.003
VF/VT (vs. PEA/asystole/bradycardia)	3.95	0.96-16.27	0.057

c-statistic: 0.669

Sens = 94%, Spec= 43%, PPV = 80%, NPV = 75%

Factors entered into model: VF/VT (vs. PEA/asystole/bradycardia), no epinephrine (vs. one or more doses of epinephrine), defibrillation attempt, ROSC prior to ED admission versus continued CPR on admission and duration of cardiac arrest (arrest to ROSC). Total cases in model = 122.

Figure 6-14 Receiver operator curve for model 1 prediction of survival status



6.5.9 Model two: Univariate and multivariate logistic regression analysis

The second model included additional variables available within four hours of PICU admission. Table 6-16 describes the univariate analysis of candidate variables. Physiological continuous variables associated with increased survival included minimum temperature and both minimum and maximum values for: pH, base deficit, lactate and glucose. Two unresponsive pupils, the requirement for continued inotropic support after resuscitation and insulin therapy were also associated with decreased survival. As expected, the paediatric index of mortality 2 (PIM2) performed well as a predictive score (Odds ratio for survival 0.04; $p < 0.001$ for a 0.1 increase in probability of death by PIM2).

Except for PIM2, all variables where $p < 0.1$ were included in a multivariate logistic regression analysis in addition to the variables identified for model one. PIM2 was excluded owing to collinearity as pupillary reaction and pH are included in the calculation of PIM2.

Table 6-17 describes the multivariate logistic regression results. Two unresponsive pupils (Odds ratio 0.19; $p = 0.001$) and increasing lactate at PICU admission (Odds ratio 0.85 $p = 0.015$) were strongly associated with decreased survival. Receiver Operator Curve of model two is illustrated in Figure 6-15. Area under the curve (C-statistic) was 0.831 and Homer Lemeshow Goodness of Fit 0.08 which is acceptable. However, because of missing values, only 105 (78%) of patients were included in model 2 using complete case selection. The model predicted death in PICU with a sensitivity of 87% and specificity of 55% (positive predictive and negative predictive value of 84% and 62% respectively).

A *post hoc* analysis was performed with the inclusion of lactate as a dichotomised variable (categorised as greater or less than 3 mmol/l at PICU admission) and removal of lactate as a continuous variable (due to colinearity with the dichotomised lactate variable). In a univariate analysis this dichotomised candidate variable was strongly associated with decreased survival (Odds ratio 0.25; $p < 0.001$). Table 6-18 describes the multivariate logistic regression model with the inclusion of lactate greater than or equal to 3 mmol/l at PICU admission and the dichotomised, no epinephrine dose (versus one or more doses) during resuscitation. In the *post hoc* analysis of model two, lactate greater than or equal to 3 mmol/l at PICU admission (Odds ratio 0.23; $p = 0.02$) and two unresponsive pupils (Odds ratio 0.29; $p = 0.04$)

were strongly associated with decreasing survival. No epinephrine (versus one or more doses) during resuscitation (Odds ratio 7.14; $p = 0.03$) was also associated with increased survival. The model predicted death in PICU with a sensitivity of 94% and specificity of 54% (positive predictive and negative predictive value of 85% and 77% respectively).

Figure 6-16 depicts the probability of survival based on the logistic regression coefficient from model 2 which included continuous lactate at PICU admission and pupillary reactivity as factors.

Using the combination of lactate level and pupillary reaction, the following prediction model was created from this sample population: Two unresponsive pupils and a lactate level on PICU admission greater than 9mmol/L or two responsive pupils and a lactate level greater than 18mmol/L both predicted a survival rate of only 10%. These cut-off points, available within four hours of PICU admission, could be used in the inclusion criteria or to stratify patients during randomisation in an RCT. Figure 6-17 shows the decision tree derived from the multivariate logistic regression model 2 and the actual number of patients in each group. This model identified 25 patients who could have been excluded owing to high probability of death with unreactive pupils and a lactate greater than 9 mmol/L; however, no patients fulfilled the second category of unreactive pupils and a lactate greater than 18 mmol/L. Only 107 patients were included in the model owing to complete case selection.

Table 6-16 Model 2: Univariate logistic regression analysis: Additional factors available after ROSC up to four hours after PICU admission (excluding those already presented in Table 6-13)

	Unadjusted Odds Ratio for PICU survival (n=155)	95% CI	P value	missing
Probability of death score by PIM2	0.04	(0.01-0.14)	<0.001	0
Minimum pH	5.32	(1.32-20.49)	0.015	9
Maximum pH	17.06	(1.49-195.24)	0.023	9
Minimum lactate (mmol/l)	0.86	(0.77-0.95)	0.004	19
Maximum lactate (mmol/l)	0.85	(0.77-0.94)	0.001	19
Minimum glucose (mmol/l)	0.87	(0.79-0.97)	0.008	10
Maximum glucose (mmol/l)	0.93	(0.87-0.99)	0.025	10
Minimum base excess (mEq/l)	1.09	(1.03-1.14)	0.001	8
Maximum base excess (mEq/l)	1.08	(1.02-1.14)	0.010	8
Minimum Temperature (°C)	1.15	(1.0-1.33)	0.051	6
Maximum temperature (°C)	1.19	(0.95-1.5)	0.133	6
Temperature < 32°C	0.42	(0.15-1.18)	0.1	6
Two unresponsive pupils	0.12	(0.05-0.27)	<0.001	23
Insulin therapy	0.46	(0.18-1.14)	0.093	1
Inotrope infusion (after resuscitation)	0.5	(0.25-1.0)	0.049	1
<i>Post hoc addition</i>				
Lactate > 3 mmol/l on PICU admission	0.25	(0.12-0.52)	<0.001	19

Table 6-17 Model 2: Multivariate logistic regression analysis of factors associated with PICU survival available up to four hours after PICU admission

Variable	Odds Ratio for survival (n=105)	95% CI	P value
Two unresponsive pupils	0.19	0.07-0.52	0.001
Maximum lactate (PICU admission)	0.85	0.75-0.97	0.015

c-statistic = 0.831 Hosmer Lemeshow Goodness of Fit test = 0.080 (df=7)
Sens = 87%, Spec= 55%, PPV = 84%, NPV = 62%

Variable in the model: VF/VT vs. PEA/asystole/bradycardia, PIM2, lowest base deficit, maximum lactate, maximum glucose, minimum pH, maximum pH, minimum core temperature, two unresponsive pupils. Total cases in model =105.

Table 6-18 Model 2 (post hoc analysis): Multivariate logistic regression analysis of factors associated with PICU survival available up to four hours after PICU admission

Variable	Odds Ratio for survival (n=100)	95% CI	P value
Two unresponsive pupils	0.292	0.09-.948	0.04
No epinephrine (vs. one or more doses of epinephrine during resuscitation)	7.14	1.22-46.96	0.03
Lactate > 3mmol/l on PICU admission	0.227	0.07-0.77	0.02

C statistic = 0.815 Hosmer Lemeshow Goodness of Fit test p=0.747 (df=3)
Sens = 94%, Spec= 54%, PPV = 85%, NPV = 77%

Variable in the model: VF/VT vs. PEA/asystole/bradycardia, PIM2, lowest base deficit, maximum glucose, minimum pH, maximum pH, minimum core temperature, two unresponsive pupils, no epinephrine (vs. one or more doses of epinephrine), lactate >3mmols on PIC admission (vs. <3mmol/l). Total cases in model =100.

Figure 6-15 Receiver operator curve for model 2 prediction of survival status

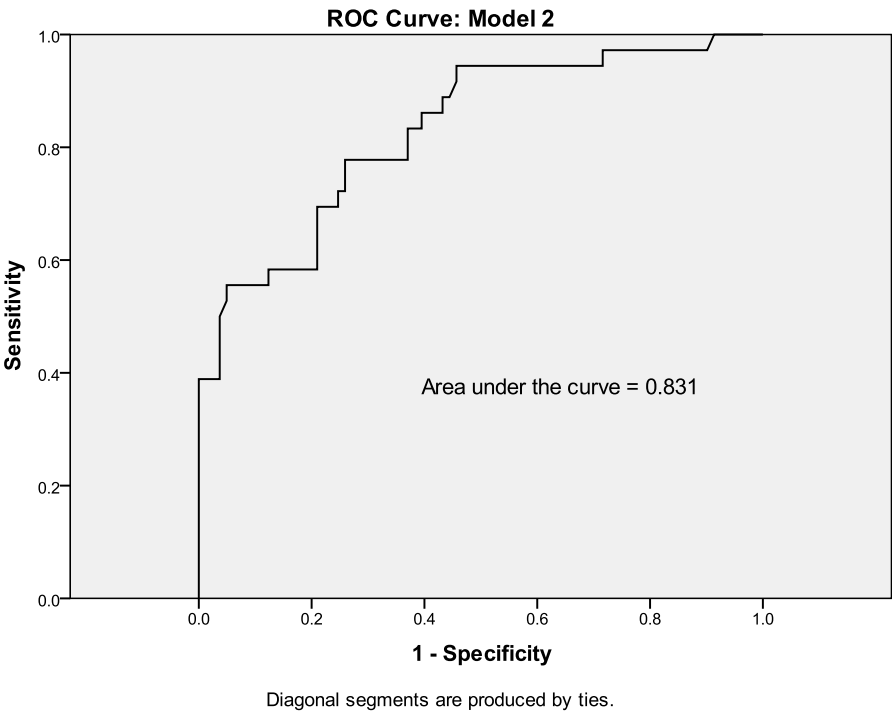
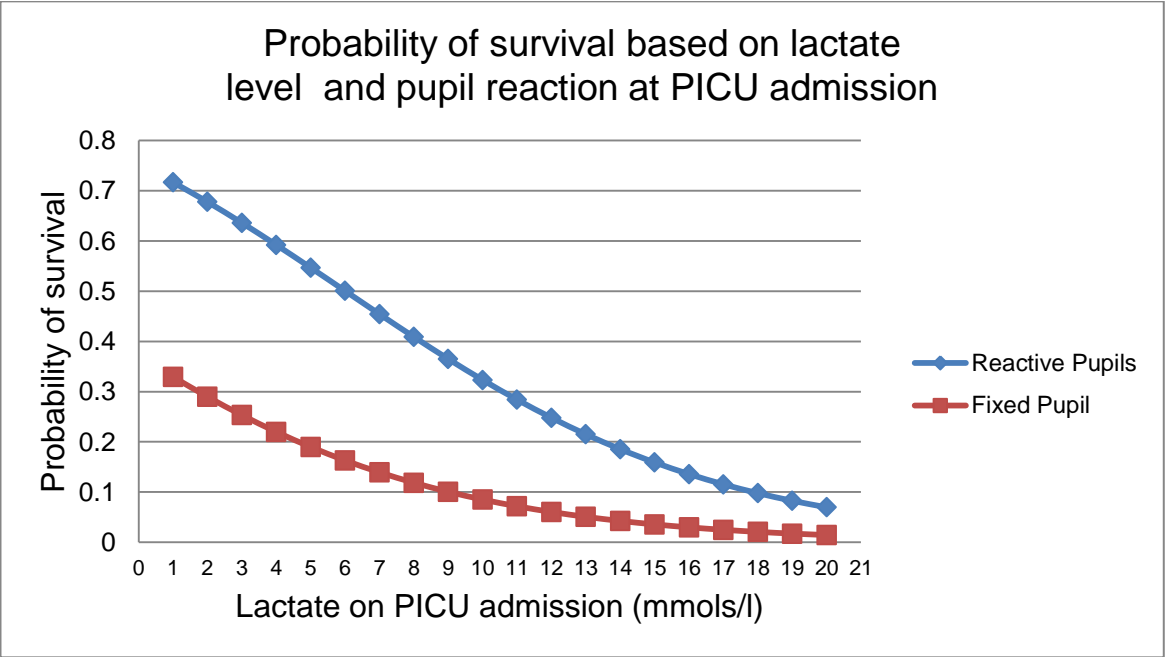
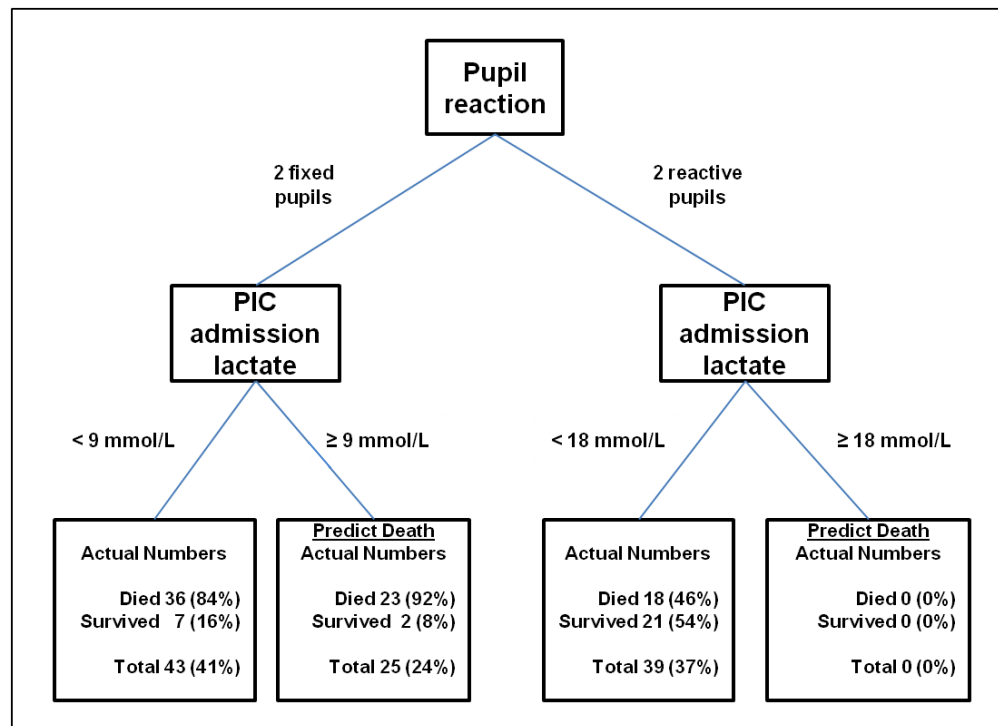


Figure 6-16 Model 2: Probability of survival based on lactate at admission to PICU



Probability model based on regression coefficient from model 2 for varying lactate level on PICU admission with either reactive or two fixed (unresponsive) pupils.

Figure 6-17 Model 2: Multivariate logistic regression derived decision tree using 10% survival as cut-off.

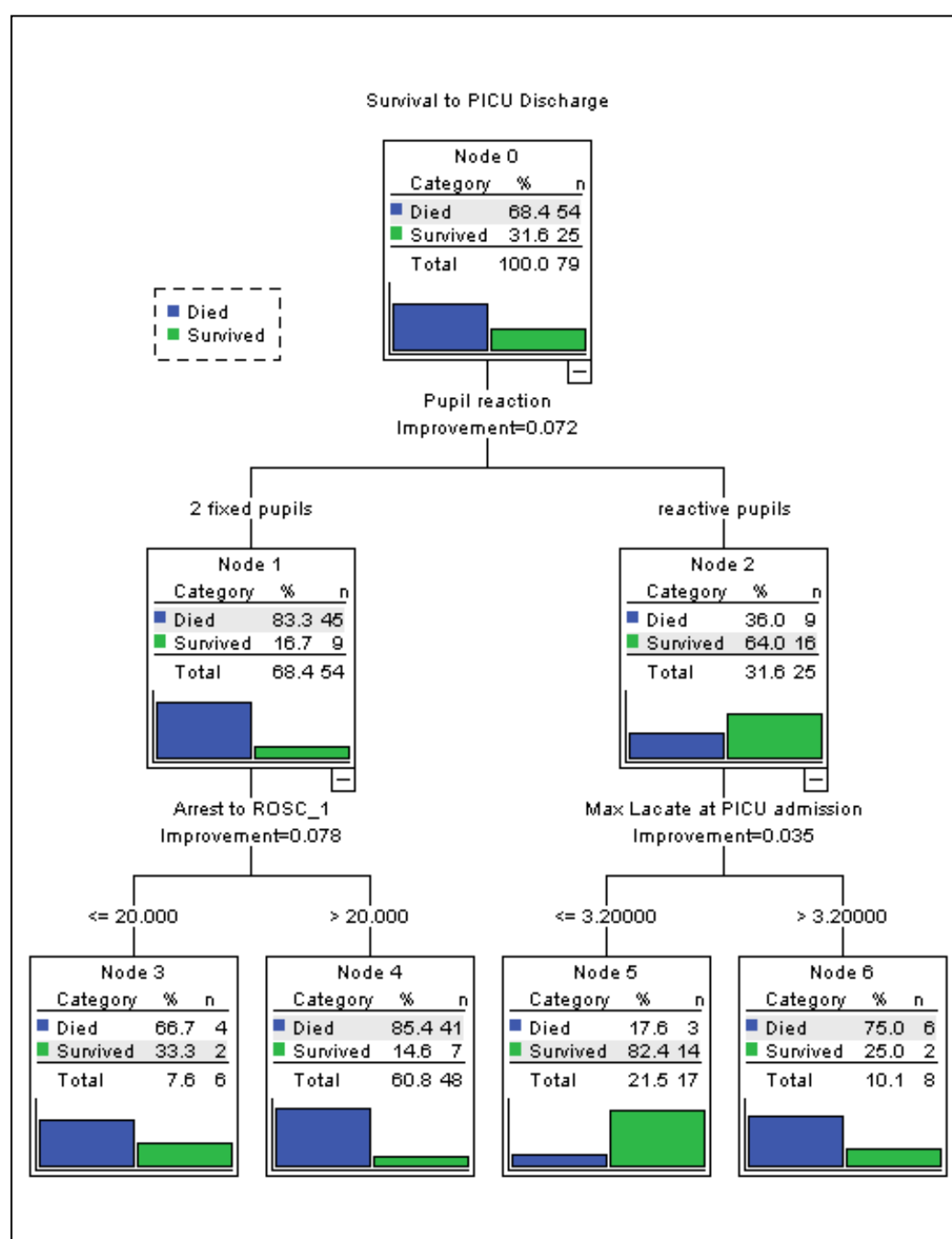


Decision model derived from multivariate logistic regression model 2. Actual numbers calculated from population sample $n = 107$. Some groups resulted in zero numbers due to the extrapolation effect of the probability curve.

6.5.10 Decision tree model: Classification and Regression Tree analysis

A decision tree prediction model was created using Classification and Regression Tree (CART) analysis with variables available during resuscitation and up to four hours after PICU admission on a random 50% of the population (Figure 6-18). The model identified pupillary reaction, duration of cardiac arrest and lactate levels on PICU admission as useful predictors. The model predicted death in PICU with a sensitivity of 87% and specificity of 64% (positive predictive and negative predictive value of 81% and 70% respectively). In this model, 85% of patients with both unreactive pupils and duration of cardiac arrest greater than 20 minutes died. The 'Risk' of the model = 0.203 therefore confirming the misclassification of 20% of cases.

Figure 6-18 CART decision tree model prediction of survival and death.



The CART tree was empirically derived from a random 50% of cases. Prediction performance figures shown relate to the test data set comprising the remaining 50% of cases. Risk of model 0.203 (SE 0.045). Data is split into segments that are as homogeneous as possible with respect to the dependent variable. Arrest to ROSC: time from cardiac arrest to return of spontaneous output (minutes). Improvement: the independent variable statistic improvement to the model by addition node.

Sens = 87%, Spec= 64%, PPV = 81%, NPV = 70%

6.6 DISCUSSION

This is the largest reported out of hospital cardiac arrest (OHCA) study in the UK paediatric population covering one quarter of all UK PICU admissions over a seven year period (2004 to 2010). The aim was to identify predictive factors of survival after OHCA in infants and children in order to potentially inform the design and analysis of future interventional trials after OHCA in the UK.

The inclusion of only patients achieving a return of spontaneous circulation after a cardiac arrest of greater than one minute and requiring admission to PICU, allowed investigation of the population most at risk of hypoxic ischaemic brain injury and considered suitable for an intervention trial (e.g. therapeutic hypothermia). The overall survival rate to PICU discharge of 32% is lower than the 50% survival identified using the PICANet data in Chapter 5; however, is very similar to the reported 38% survival to hospital discharge rate by Moler et al (2011). The Moler study also found that age, bystander CPR and witnessing of arrest were not associated with survival. Predictive factors for survival to PICU discharge in the current study were identified by univariate logistic regression analysis. Factors associated with survival, available prior to cardiac arrest or during resuscitation, included: presenting in a shockable rhythm (VF or VT), shorter duration of cardiac arrest, return of spontaneous cardiac output prior to arrival in the emergency department and lower number of epinephrine doses. Additional factors associated with survival, available within four hours of PICU admission, included: higher pH, lower lactate, lower maximum glucose, higher base deficit, lower PIM2 score and two reactive pupils.

After the primary multivariate logistic regression analysis, the only factor independently associated with survival available before cardiac arrest or during resuscitation was presenting in a shockable rhythm (VF/VT). *Post hoc* analysis identified the addition of no epinephrine versus one or more doses of epinephrine during resuscitation as a factor associated with survival which was also identified by Moler et al (2011). With the inclusion of variables available at the time of PICU admission, factors strongly associated with decreased survival included high blood lactate level and two unresponsive pupils. *Post hoc* inclusion of the dichotomised epinephrine dose (no epinephrine versus one or more doses of

epinephrine during resuscitation) and dichotomised lactate level (greater than or equal to 3mmol/L versus less than 3mmol/L) at PICU admission changed the model and identified the association of two unresponsive pupils and higher plasma lactate within four hours of PICU admission with decreased survival and no epinephrine dose at resuscitation with increased survival. The CART decision tree analysis created a similar model identifying the use of either the duration of cardiac arrest or lactate level on PICU admission depending on pupillary reaction response. Performance of the prediction models one and two improved with the addition of physiological factors available within four hours of PICU admission. The CART decision tree and prediction model two were comparable with respect to sensitivity, specificity, positive and negative predictive values.

6.6.1 Shockable rhythm

In this study, 12% of patients with ROSC and admission to PICU presented in a shockable rhythm (either VF or VT) and this was associated with increased survival. The survival benefit of presenting in VF or VT has been identified in a number of OHCA studies (Young et al, 2004; Herlitz et al, 2007; Hickey et al, 1995; Mogayzel et al, 1995; Smith et al, 2006). Although, the true incidence of VF/VT in the paediatric OHCA population is not clear. Atkins et al (2009), in a large multicentre, registry study, identified 7% of patients with a shockable rhythm (ranging from 4 to 5% of infants and 15% of adolescents), though in 7% of patients this information was missing and in a further 11% the rhythm was un-interpretable. This is comparable with our current study, where the presenting cardiac rhythm was not recorded in 10% of patient's case notes. However, our study confirms the importance of early identification of cardiac rhythm in the paediatric patient by first responders and emergency department staff.

6.6.2 Duration of cardiac arrest

Increased duration of cardiac arrest as a predictive factor for increased mortality has been described by many. Schindler et al (1996) studied children presenting after OHCA to an emergency department and reported no neurologically intact survivors following ongoing resuscitation in the emergency department, greater than 20 minutes. In that study, median duration of resuscitation in the emergency department for survivors was 9 minutes (range 6-

18 minutes) versus 20 minutes (range 6-115 minutes) for non-survivors. In our study, 1 in 4 patients with 21-30 minutes of CPR in the emergency department, who achieved a ROSC, survived. Improvement over the last two decades in resuscitation practices, pre-hospital care and post-intensive care management may all be potential factors in this finding. Interestingly, total duration of cardiac arrest or ROSC prior to emergency department admission was not independently associated with survival in the multivariate logistic regression model. However, duration of cardiac arrest was identified in the CART analysis decision tree for the group of patients with two fixed and unreactive pupils. In this subgroup of patients with two fixed pupils, a duration of cardiac arrest greater than 20 minutes resulted in death before PICU discharge in 85% of cases in the test sample. Our inclusion of only patients with ROSC will increase the observed difference noted between Schindler et al (1996) and this study, as there will be a number of OHCA patients not achieving ROSC in the emergency department who were not included in this study.

Circumstances where prolonged resuscitation is suggested by international resuscitation guidelines include OHCA secondary to cold water near-drowning (Soar et al, 2010). In our study 12 patients were successfully resuscitated after near drowning. Median duration from cardiac arrest to ROSC in the drowning population was 54 (IQR [32 to 126]) minutes with continued resuscitation in the emergency department from arrival for 38 (IQR [9 to 82]) minutes; although survivors had shorter durations for both total and emergency department resuscitation times. All survivors in this group were hypothermic (less than 32°C) on arrival and these findings support the need to treat this population differently as hypothermic neuro-protection at the time of cardiac arrest may allow potential recovery despite a prolonged period of resuscitation (Soar et al, 2010).

6.6.3 Epinephrine use

The use and timing of epinephrine during OHCA resuscitation is described clearly in resuscitation algorithms (Biarent et al, 2010). This study identified that only 29% (14/50) survivors did not receive any epinephrine and there was a marked fall in survival rate from 75% to 30% when any epinephrine was required. Moler et al (2011) found just over half (52%) of survivors in their study did not receive epinephrine and reported a very high

mortality (96%) in patients receiving three or more doses. Our study does not support this finding. As was found with prolonged resuscitation times, survival rates in patients receiving four, five or even six or more doses of epinephrine remained around 20 to 25% and therefore a resuscitation cut-off at the suggested level of three doses would not be appropriate based on our data.

6.6.4 Length of time to PIC admission

This study confirmed the finding from Chapter 5 that 74% of patients required transportation from another hospital into the PICU. As a result, time to admission from ROSC was considerable for both survivors and non-survivors and was a median of four hours 30 minutes. An important finding was that individual emergency department's exposure to successfully resuscitated OHCA patients was infrequent. 111/150 patients transported to PICU were transported from 61 different emergency departments; therefore, each emergency department only transferred a median of one patient over the whole seven year period. These findings have important implications for potential post cardiac arrest trial design. Evidence supports the need for therapeutic hypothermia to commence as soon as possible after cardiac arrest. Previous hypothermia studies that demonstrated a benefit to neurological outcome in either adults or neonates (Bernard et al, 2002; HACA, 2002; Azzopardi et al, 2009), have advocated commencement of therapeutic hypothermia within six hours. The optimum therapeutic window in infants and children is not known but could theoretically fall within this time frame. Practical considerations in trial design include when and how patients can be enrolled into studies, when and how consent can be obtained and whether it is feasible for temperature management to begin early after ROSC. One option would be to prospectively obtain informed consent of parents of OHCA patients on arrival at the admitting PICU. However, the opportunity for families to be approached and to consider the implications of the trial will be severely limited given the importance of early initiation of therapy. A second option, which requires emergency medicine teams to recruit patients at the initial presenting hospital, risks potentially investing time and money in supporting a large number of emergency departments which will probably admit only one or two patients during the whole study period. A third, more efficient recruiting option, would be to utilise the

specialist retrieval services, which are now established, and transport patients from emergency departments to the PICU. This would significantly minimise the number of personnel involved in delivery of the trial protocol, maximise expertise and allow earlier recruitment and enrolment within the therapeutic time period before PICU admission.

6.6.5 Blood lactate level

Blood lactate level at PICU admission was significantly lower in survivors and a strong predictor of survival after OHCA in our study. This is similar to Kliegel et al (2004), who reported adult survivors after OHCA had lower lactate levels on emergency department admission (median, 7.8 mmol/L (IQR, 5.4-10.8) versus non-survivors 9 mmol/L (IQR 6.6-11.9). Donnino et al (2007), in a retrospective study of successfully resuscitated adults after OHCA, found similar lactate levels between survivors and non-survivors on emergency department admission. However, in a multivariable analysis, they found high lactate clearance at 12 hours was significantly associated with early (24 hour) survival ($p < 0.05$). (Donnino et al, 2007). Lactate has also been identified as an important predictive factor in all PICU patients, adding to the performance of the PIM2 score (PICANet, 2011). Moler et al (2011) excluded lactate from their logistic regression because of missing values. In our study, lactate was not available immediately after ROSC and was only infrequently measured in the emergency department (35% (54/155) of patients). We therefore utilised the score available up to four hours after admission to PICU. This may therefore reflect improvement in clearance of lactate over time from ROSC to PICU admission in survivors; however early, post-ROSC lactate levels were not available for comparison. Lactate is a marker of anaerobic metabolism and reflects ischaemic stress. It has been identified as a predictor of survival after sepsis, septic shock, cardiac bypass (Allen, 2011; Hatherill et al, 2000; Mikkelsen et al, 2009; Siegel et al, 1996) and is likely to reflect the pathophysiological damage occurring before, during and after resuscitation. For example, preceding conditions such as asthma may result in high lactate levels due to tissue hypoxia compared to a sudden cardiac arrhythmia. During resuscitation, better CPR may also increase lactate levels due to tissue washout phenomenon. Lactate levels can also be increased by excess epinephrine administration or microcirculatory failure (Al Thanayan et al, 2008). Despite

these confounding issues, high PICU admission lactate was predictive of survival outcome in this cohort and became incorporated in both the multivariate logistic regression model 2 and the CART analysis. We therefore recommend that blood lactate level is included in risk-stratification criteria for prospective interventional studies.

6.6.6 Temperature

Temperature variation and relationship to survival after cardiac arrest is of considerable interest. In this study, temperature was infrequently recorded on arrival to the emergency department or at the time of ROSC. However, in 42% of patients with recorded temperatures, there was no difference in temperature between survivors and non-survivors. At the time of leaving the emergency department the difference in temperature between survivors and non-survivors was approaching significance (35.9 (IQR [34.9 to 36.5])°C vs. 34.7 (IQR [33.2 to 36.3])°C; $p=0.051$). By PICU admission survivors were 1°C warmer (36.5 (IQR [35.6 to 37.2])°C) than non-survivors (35.5 (IQR [33.4 to 37.0])°C; $p=0.007$). In our study, patients admitted after near-drowning were included ($n=12$). The median lowest recorded temperature in the emergency department for the near-drowning population was 27.3 (IQR [26 to 30.3], range 14 to 35.8)°C. Only two patients after near-drowning had a minimum temperature greater than 32°C and neither survived.

During the analysis of temperature as a candidate variable for survival prediction, a number of important confounders were identified. Patients who required transportation from a different emergency department demonstrated an increase in temperature from the emergency department to PICU admission compared to patients admitted directly from the emergency department to PICU, who showed a fall in temperature. Those transported had a significantly longer time period between the emergency department and PICU admission and opportunity for spontaneous rewarming, or application of warming measures. Patients who subsequently received therapeutic hypothermia in PICU tended to decrease their temperature between the emergency department and PICU admission compared to those who eventually received standard therapy; although, this difference was only seen in the patients who were transported. These observations may imply that transport teams were

already aware of the targeted temperature approach and either actively cooled, or actively avoided warming patients during the transport.

6.6.7 Hypothermia

Spontaneous hypothermia after cardiac arrest has been observed in both paediatric and adult studies (Lyon et al, 2010; Hickey et al, 2000; Takino & Okada, 1991; Fink et al, 2010). The median minimum temperature in the first 12 hours after OHCA in the study by Meert et al (2009) was 34.1 (IQR[32.5 to 35.6])⁰C and would not have been influenced by subsequent therapeutic hypothermia (as only used in 3/138 patients). Comparing the survivors and non-survivors of the same population, Moler et al (2011) identified survivors had significantly higher, minimum temperatures by 2⁰C in the first 12 hours after ROSC compared to non-survivors (35.5 (IQR[33.7 to 36.2])⁰C vs. 33.5 (IQR[32.3 to 34.8])⁰C; $p>0.01$). Compared to our study, minimum temperature after ROSC to four hours after PICU admission was very similar for both sets of non-survivors (33.3⁰C vs. 33.5⁰C); however median temperature for survivors in Moler et al (2011) was higher by 1⁰C (35.5⁰C vs. 34.5⁰C). This might have been explained by the greater use of targeted temperature therapy causing a reduction in median minimum temperatures in our study.

6.6.8 Hyperthermia

The association of hyperthermia after brain injury and poor neurological outcome or death has been repeatedly observed after cardiac arrest (Bembea et al, 2010; Suffoletto et al, 2009; Hickey et al, 2000; Zeiner et al, 2001). International resuscitation guidelines have therefore repeatedly stressed the need to avoid hyperthermia after paediatric cardiac arrest (ILCOR, 2006; Kleinman et al, 2010). Therefore, identifying 29% (45/155) who experienced hyperthermia (temperature greater than 38⁰C) within the first 24 hours is a concern, as all but one episode of hyperthermia occurred after PICU admission. Although this was not associated with a significant effect in survival, it is possible that unmeasured neurodevelopmental injury may have occurred. The proportion of hyperthermic patients identified signifies that recommendations pre-dating the start of this study were not followed; however, the reason for this is not clear from this study and will require further evaluation.

Median, maximum temperatures measured only in the emergency department, or with inclusion of temperature up to four hours after PICU admission, were similar for survivors and non-survivors.

Comparison of median temperatures every four hours after PICU admission up to 24 hours did not show an increase trend in temperature in either survivors or non-survivors. Rebound hyperthermia has been noted to occur 6-12 hours after successful resuscitation in patients not undergoing active targeted temperature control (Takino & Okada, 1991; Hickey et al, 2000; HACA, 2002) and in the control (standard therapy) arm of the European Hypothermia after Cardiac Arrest randomised control trial (HACA, 2002). Bembea et al (2010), identified that fever in the first 24 hours was associated with worse outcome. However, the time window for vulnerability is not clear. In an animal study, fever at 24 hours but not 48 hours was associated with increased CA1 hippocampal cell death (Hickey et al, 2003). Bembea et al (2010) interestingly reported that “any hyperthermia” after adjusted multivariate analysis was associated with a non-significant trend towards better neurological outcome and survival versus children with no hyperthermia. In an editorial accompanying this report (Fink, 2010), it was postulated that pre-conditioning with hyperthermia prior to arrest may have influenced this finding (although without supportive pre-arrest temperature data this is only speculative). However, this hypothesis is supported by animal studies where pre-conditioning hyperthermia induced heat-shock protein 70 and reduced brain injury in rats that were subsequently exposed to ischaemia at normothermia (Chopp et al, 1989; Ota et al, 2000).

This study has identified the occurrence of both severe hypothermia ($<32^{\circ}\text{C}$) and hyperthermia after OHCA in children and the association of severe hypothermia with increased mortality. Overall, temperature recording was infrequently performed or recorded, especially in the emergency department. This may be as a result of lack of awareness of the importance of temperature management after OHCA or as a result of the retrospective design of this study relying on documentation of information. The difference in the proportion of patients receiving targeted temperature management across the three PICUs is consistent with the observations in Chapter 4 which reported the variation in use of the

therapy by UK, paediatric intensive care consultants. The main implications of this finding, with respect to the current study, will be to include only Unit 2 patients when comparing outcomes of therapeutic hypothermia versus normothermia (Chapter 7). Inclusion of Unit 1 and Unit 3, who have very small populations receiving therapeutic hypothermia, has the potential to introduce additional confounding variables and reduces the ability to extract the observed differences between the two potential treatments. With regards to future interventional RCTs, considerable efforts will be required to improve the temperature monitoring in the emergency department and procedures for temperature control to ensure standardisation of practice and compliance with prospective temperature monitoring and control protocols.

6.6.9 Extracorporeal life support

ECLS was used in only three patients during this study. One patient requiring full cardiac support and rewarming for extreme hypothermia and two, after a period of ROSC, for poor cardiac function and hypoxia. One survived to PICU discharge but was discharged to a hospice for terminal care and died a few days later. The use of ECLS during resuscitation in patients who do not regain ROSC (known as extracorporeal life support CPR or ECPR) has become an established tool in refractory in-hospital cardiac arrest and in cases of severe hypothermia. In selected cases survival with good neurological outcome has been reported in 30-40% of patients (Huang et al, 2012; Joffe et al, 2012). Its use in the OHCA population is much more controversial owing to the poor survival outcomes and has been described by only a few adult centres (Kagawa et al, 2010). Recently though, a preliminary report of a ten-fold increase in neurologically intact survival where ECPR has been used for refractory VF cardiac arrest in Japanese emergency department has been announced (Asai et al, 2012). Although promising, further analysis of these findings will be required when published in full. ECPR, unfortunately, is an extremely expensive resource and likely to only be available in tertiary teaching hospitals.

6.6.10 Limitations: Neurological outcome

Survival with a good neurological outcome is the major target of resuscitation and post-resuscitation therapy. Very poor neurological outcome will be regarded as worse than not-

surviving by some families. A major limitation to this study was the lack of neurological outcome data. The original plan was to calculate the Paediatric Cerebral Performance Category (PCPC) score at PIC discharge and hospital discharge. Because of the methodological constraints of the study, data were only extracted from medical records. Unfortunately, only limited information relating to neurological function could be obtained from medical records and clinic letters and in a number of cases, where patients were transferred back to their referring hospital, no follow-up data were available. Therefore, with only limited PCPC data available, it was not possible to accurately report or analyse. Because of the importance of this information, a full Regional Ethics Committee application has now been submitted with a view to contacting families of surviving infants and children of all three hospitals to undertake a follow-up study to supplement the results of this study.

6.6.11 Limitation: Missing data

An inherent problem of retrospective medical studies is missing data and this study is no exception. Firstly, the missing cases identified as potential OHCA patients from Unit 3, weakens the overall conclusions and risks introducing case selection bias, especially as the case notes of deceased patients are generally easier to access and review. This may explain why Unit 3 had the lowest reported survival rates. The second problem regarding missing data was in the situation when medical records were available but data was missing from them. One example is the lack of blood lactate measurements in the emergency department, when other blood gas parameters (pH, base deficit etc) were recorded. This is possibly because blood gas analysers did not include lactate measurement as standard. The lack of recorded core temperatures in the emergency department may be due to either the temperature not being taken or taken and not recorded, but for what reason? Was the temperature not taken because the patient 'felt' warm enough which would therefore raise the study population's mean/median values, or was it just not considered even if the patient was cold? If the temperature was taken and not felt to be important, was it therefore also not recorded? This study is unfortunately not able to answer these questions, but it should be considered for future trial implications. A final scenario is that missing data, such as aetiology of OHCA, is likely to represent the inherent difficulties associated with identifying a

cause of arrest in this population. Although, our missing data rate, in this respect, is comparable to other retrospective and prospective cardiac arrest observational studies.

The consequence of missing data was most notable in the multivariate logistic regression analysis. In this study, we elected to handle missing data by not imputing or substituting by mean or regression approaches (White & Carlin, 2010). In the multivariate logistical regression models, complete case selection (or listwise deletion as defined in the SPSS statistical package) of cases was adopted, therefore including only cases with all included variables. The disadvantage to this approach is that the sample size is reduced, the potential for type I and II errors are increased and the model may not accurately represent the whole study sample or the general population. Both multivariate logistic regression model 1 and 2 included only 65-77% of complete case. We were reassured by the finding that both model results remained consistent if only the final identified variables were used in a repeat forward step-wise analysis (which allowed an increased number of cases to be included). However, owing to most of the variables included in the model being closely correlated to each other, there is the potential for the model to change and produce different strongly associated factors with only a few additional cases. The advantage to our complete case selection approach was that we were not creating new values which may reinforce wrong assumptions of the logistic regression models and is the method most favoured in recent guidance (Groenwold et al, 2012; White & Carlin, 2010). This is especially important in view of the small overall sample size of our study population and as mentioned, the close correlation of candidate variables.

Our missing data rates were comparable with other published studies. The multicentre registry study (National Registry of Cardiopulmonary Resuscitation) had incomplete data on presenting cardiac rhythm in 22% of cases (Nadkarni et al, 2006), the large North American study by Young et al could not report aetiology in 11% of cases and Moler et al (2010) had missing data for a large proportion duration of total cardiac arrest and lactate levels and omitted them from their analysis. The solution to the problem of missing data may be the use of prospective collected, protocolised, specific clinical data.

6.6.12 Limitation: Study size

A strength of this study was the inclusion of a large population from three large UK PICUs, accounting for 23% of all PICU admissions in the UK. However, the study required data collection over a seven year period and changes in resuscitation management, patient PIC admission criteria and PIC post-cardiac arrest care may have influenced outcome. We found no change in the proportion of survivors over the time period although post-cardiac arrest interventions changed. Although the study accounts for nearly a quarter of all patients in the UK and findings were consistent with other published studies, there is a possibility that case selection and management of OHCA patients in these PICUs is not representative of the rest of the UK. In addition, we identified differences between the three units included within the study. For example, unit one did not have an emergency department co-located with the PICU, therefore, all their patients required transportation thus delaying time to admission. As previously stated, there was also a significant difference in the proportion of patients receiving therapeutic hypothermia and targeted temperature management on PICU. Although, overall survival rates across the three units were not significantly different.

6.6.13 Limitation: Pre-hospital management and CPR quality

Owing to the retrospective nature of this study and the focus on emergency department and PICU data collection, limited data was available regarding pre-hospital management of paediatric patients prior to emergency department admission. As identified in this study only 8% of children achieved a ROSC prior to admission to the emergency department; however, it is not possible to ascertain the reasons why ROSC was achieved after arrival but not during pre-hospital care. This critical and challenging time pre-hospital is potentially a vital period where reduction of further ischaemia reperfusion injury can be achieved. However the risk to benefit ratio between implementing advanced life support techniques and resultant delays in transporting patients is extremely difficult to balance. Assessment of paramedic and ambulance crew interventions for OHCA including both patients who do and do not achieve ROSC will be required in a future study. This may potentially identify further areas for improving our outcome prediction models or more importantly cardiac arrest survival.

6.6.14 Limitation: CART analysis

The prediction tool created in this study using CART was a balance between simplicity and accuracy. Multiple adjustment settings to the decision tree are possible in its creation and the use of a training and test sample reduced further the size of the population to create the tree. Therefore, caution regarding the applicability of the findings to other OHCA populations or individuals must be stressed.

6.7 CONCLUSION

Through the collection of the largest study population of infants and children achieving ROSC and admission to PICU after OHCA, this study has identified multiple factors associated with PIC survival. We confirmed the importance to survival of identifying and treating a shockable rhythm during resuscitation in the paediatric population and identified the strong association with mortality of raised blood lactate level and two unresponsive pupils on admission to PICU. Analysis of the resuscitation variables of patients admitted to PICU has also informed key areas of trial design, including: baseline mortality rates, timing and opportunity for recruitment and consent, current variability in temperature monitoring, variability in targeted temperature management, and factors strongly associations with mortality. The prediction model could be used as a risk-stratified randomisation or analysis tool in a future RCT, in addition to setting inclusion/exclusion criteria to remove patients likely to die despite any potential post-resuscitation intervention. This would increase the efficient use of a clinical trial study population, reducing the number of patients required and maximising research cost-utility.

Table 6-19 Chapter 6 and RCT feasibility

What have we learnt from this study towards the feasibility of a UK randomised controlled trial?

Only a third of patients admitted to PIC after OHCA survive to PICU discharge. This is comparable with published studies; however, lower than the estimate from the NETPACK study (Chapter 5).

Presenting rhythm and need for epinephrine during resuscitation, plus high lactate and presence of two unresponsive pupils at PIC admission, are key associated factors with poor survival in this population and will need to be factored into the design of an RCT. A potential decision tree model is presented.

Median time to PICU admission after OHCA is four and a half hours and may involve transfer from a large number of referring hospitals. Early recruitment will require additional input by specialist transport teams.

There was wide variation in the proportion of infants and children receiving therapeutic hypothermia amongst the three PICUs in this study.

6.8 ACKNOWLEDGEMENT

I acknowledge the efforts of the following individuals who assisted with data collection and entry at the three study site (Table 6-20).

Table 6-20 List of data-collectors for each PICU

Unit	Data collector
Birmingham Children's Hospital	Dr Barney Scholefield (Chief investigator)
	Miss Jessica Gosney
	Miss Victoria Sanders
	Dr Richard Skone
Alder Hey Children's Hospital	Miss Felicity Haigh
	Dr Nayan Shetty
	Dr Peter Fitzmaurice
Great Ormond Street Hospital	Dr Sainath Raman
	Dr Alex Hussey
	Dr Sophie Skellett

In addition to the clerical support gathering medical records of Mr Kashif Ali and Ms Hayley Osmani at Birmingham Children's Hospital.

6.9 CONTRIBUTORSHIP

Dr Scholefield (BS) designed the current study protocol, data collection tool and database. Data collection was performed by a team of data collectors (Table 6-20). Data cleaning, validation and queries were performed by BS. All statistical analysis and drafting of chapter content was performed by BS. Dr Paul Davies provided statistical advice. Study design and Interpretation of data was performed with supervisory assistance from Drs Morris & Duncan, Prof Gao-Smith, Drs Skellett & Peters (Great Ormond Street). Final draft of chapter was additionally reviewed by Prof Perkins.

7 Comparison of the use of therapeutic hypothermia with standard temperature therapy after paediatric out of hospital cardiac arrest.

She tasted the porridge from the first bowl.

“This porridge is too hot!” she exclaimed.

So, she tasted the porridge from the second bowl.

“This porridge is too cold,” she said

So, she tasted the last bowl of porridge.

“Ahhh, this porridge is just right,” she said happily and she ate it all up.

Goldilocks and the Three Bears: Robert Southey (1837)

7.1 ABSTRACT

7.1.1 Introduction

Therapeutic hypothermia (TH) may improve survival and reduce brain injury for children after out of hospital cardiac arrest (OHCA). International resuscitation recommendations to consider TH were adopted by our tertiary paediatric intensive care unit (PICU) in 2007. Evaluation of patient temperature management and outcomes may inform the feasibility of performing future TH trials and its potential benefits or harm in children.

7.1.2 Aims

To assess the benefits and safety of TH (core temperature 32-35°C) versus standard temperature management (ST) (>35°C) after paediatric OHCA.

7.1.3 Methods

Retrospective cohort study set in a UK tertiary PICU. Infants and children greater than 24 hours until their 16th birthday admitted to PICU after an OHCA (January 2004 to December 2010).

7.1.4 Results

We studied 73 patients admitted to PICU after out of hospital cardiac arrest. Thirty eight patients (52%) received TH. Compared to ST, the TH group received more bystander CPR (80 vs. 47%; $p=0.005$), a trend towards longer duration of cardiac arrest (40mins (27-58) vs. 30mins (22-48); $p=0.264$) and a lower core temperature at PIC admission (34.3°C vs. 36.1°C; $p=0.007$). In patients receiving TH, return of spontaneous circulation to target temperature duration was 5.5hrs (1.5-8hrs). If core temperature was >35°C ($n=18/36$) at the start of TH induction, target temperature was reached within 2.5 hrs (2-4hrs) at a rate of 0.9°C/hr (0.5-1.5). Median TH target temperature was 33.5°C (33-34°C) for a duration of 23 hours (17-25hrs). Rewarming lasted 10hrs (6.5-15hrs) at a rate of 0.3°C/hr (0.23-0.45). There was no difference in hospital survival (TH: 34% vs. 23% ST; $p=0.284$). TH group had

a significantly longer PICU length of stay (4.1 days [3.0-6.8] vs. 1.3 day [0.5-6.7]; $p<0.001$).

All patients experiencing a core temperature $<32^{\circ}\text{C}$ died.

7.1.5 Conclusions

This is the first UK and largest study comparing the use of TH with ST after OHCA. TH was effectively administered in the paediatric population with limited adverse events; however, it did not increase survival to hospital discharge. Further prospective evaluation is warranted.

7.2 INTRODUCTION

Therapeutic hypothermia (TH) may be a treatment which improves survival and reduces brain injury for children after out of hospital cardiac arrest (OHCA). The 2010 International liaison committee on resuscitation (ILCOR) recommendations state: 1) TH (32 to 34°C) *may be beneficial* for adolescents who remain comatose following resuscitation from sudden, witnessed, out-of hospital, VF cardiac arrest and 2) TH (32 to 34°C) *may be considered* for infants and children who remain comatose following resuscitation from cardiac arrest (Kleinman et al, 2010). The evidence to support the recommendations for TH by ILCOR is based on extrapolation of neonatal and adult RCTs, as no paediatric RCTs have been published. However, neonatal studies were performed on patients after hypoxic ischaemic encephalopathy where cardiac arrest often did not occur and the adult studies were performed in a group of patients specifically presenting in a shockable rhythm (ventricular fibrillation or ventricular tachycardia). Therefore, there remains a strong need for additional paediatric evidence regarding TH to inform clinical practice.

There is some limited paediatric specific observational evidence as described in detail in the Cochrane systematic review (Chapter 3) but this evidence lacks essential information regarding paediatric post cardiac arrest management pertinent to future trial design. Only two retrospective observational studies (Fink et al, 2010; Doherty et al, 2009) and one (unpublished) prospective observational study (Buttram et al, 2009) compared TH with standard therapy (ST) in the paediatric population. None of the observational studies demonstrated a significant difference in paediatric cardiac arrest survival or the proportion with good neurological outcome when treated with TH. The main limitations of these studies included; small numbers, relatively old studies (before and after the publication of the two main RCTs supporting TH in adults (Bernard et al, 2002; HACA, 2002), unbalanced groups with regards: increased severity of illness, use of extracorporeal life support (ECLS) and higher propensity scores associated with TH use. Also the majority (95%) of patients in the Doherty et al (2009) study were after in-hospital arrests as were 50% in the study by Fink et al (2010). There was also a lack of reporting of data with regards; time delay to admission, route of admission (e.g. from another hospital), transportation time, time to initiate TH, time

to reach target temperature and physiological differences between paediatric patients treated with TH and ST. All these factors would be potentially useful in future trial design and feasibility of performing a prospective interventional study in this population.

Although overall adjusted mortality and neurological outcomes for patients receiving TH and ST were similar in both studies, important additional observations regarding temperature control were identified. Fink et al (2010) reported that inadvertent hypothermia ($<32^{\circ}\text{C}$) in the TH group was associated with increased in-hospital mortality. They also reported a high rate of hyperthermia ($>38^{\circ}\text{C}$) although not associated with worse survival outcome. Inadvertent overcooling has also been identified in adult (Merchant et al, 2006), paediatric (Topjian et al, 2011) and neonatal (Sarkar & Barks, 2010) hypothermia studies and remains an area of concern requiring accurate temperature control during therapy application (Polderman & Herold, 2009). Further evaluation of temperature control and application of TH in the paediatric population is therefore important.

The ILCOR recommendations, based on the adult and neonatal evidence, to consider TH after paediatric cardiac arrest, were adopted by our tertiary paediatric intensive care unit (PICU) in January 2007. Paediatric Intensive Care consultants had the autonomy to decide whether to use targeted temperature management in addition to routine post-cardiac arrest care. 24 hours of TH at a temperature of $32\text{--}34^{\circ}\text{C}$ with gradual rewarming was generally adopted as per ILCOR guidance, although a formalised treatment protocol was not published until November 2009 explicitly stating the desired duration of 24 hours, a temperature target of 33°C and a rewarming rate of 0.25°C per hour. Prior to January 2007 and in patients after 2007 not receiving TH, standard temperature therapy (ST) after OHCA in our PICU followed recommended best practice which involved maintaining normothermia ($36.5\text{--}37.5^{\circ}\text{C}$) and avoiding hyperthermia ($>38^{\circ}\text{C}$).

An evaluation of the post cardiac arrest management and eventual outcomes of patients receiving TH compared to patients receiving ST will inform the potential effect of the therapy on survival in the post OHCA population. In addition, valuable information will be obtained to inform the feasibility of designing a post cardiac arrest intervention study using targeted temperature therapy. This includes data on implementation of therapy, time to reach target

temperature, stability and rewarming rate. Adverse event rates and the difference in physiological responses to TH versus ST will also be available.

7.3 AIMS

7.3.1 Primary Aim

1. To ascertain hospital survival rates in children receiving therapeutic hypothermia (TH) and compare with those receiving standard temperature management (ST) after paediatric out of hospital cardiac arrest.

7.3.2 Secondary Aims

1. Evaluate time to commencement, rate of cooling, duration, depth, stability and rate of rewarming of administered TH.
2. Assess adverse clinical and physiological effects of TH.

7.4 METHODOLOGY

7.4.1 Settings and participants

This retrospective, single-centre, cohort study included infants and children admitted to the PICU at Birmingham Children's Hospital after out-of-hospital cardiac arrest (OHCA) over a seven year period (Jan 2004- Dec 2010). Data were collected in conjunction with the multi-centre study described in Chapter 6 with additional data regarding targeted temperature management and physiological parameters.

Birmingham Children's Hospital PICU is a large, regional paediatric centre admitting 1300 infants and children per year. National and local databases identified potentially eligible patients. These included the PICANet admission coding for preceding cardiopulmonary resuscitation (CPR) and preceding hospital cardiac arrest, local PICU discharge coding system for terms relating to cardiac arrest and out-of-hospital cardiac arrest, and an existing cardiac arrest and acute life threatening events registry.

7.4.2 Study design

Inclusion: Patients aged 24 hours old, up to their 16th birthday, admitted to PICU after an OHCA with successful return of spontaneous circulation were included. OHCA was defined as no cardiac output and pulseless for greater than one minute as confirmed by a trained medical practitioner/paramedic prior to arrival at an emergency department.

Exclusion: Patients were excluded if they were younger than 24 hours of age or had an OHCA secondary to birth asphyxia. This age limit was to exclude patients admitted after perinatal hypoxic ischaemic encephalopathy, as standard treatment protocols regarding the use of TH are already established and this patient population is admitted to a neonatal intensive care unit separate from our PICU.

7.4.3 Data collection and assessment

Retrospective reviewing of individual case notes, PICU nursing charts and computerised patient records was performed. Data were recorded electronically onto a piloted Excel (Microsoft, USA) spreadsheet and inputted, analysed and saved securely within the NHS

Trust fire-walled computer server. A data-entry guide and instruction booklet was created. One to one training was provided for three data collectors (Ms Gosney, Sanders and Dr Skone) by the chief investigator. Inputted data was verified at the inputting stage using data-verification limits set in the excel programme which generated a warning message for values outside expected ranges (e.g. age limit set to 0-16 would alarm and not allow recording if values greater than 17 were entered). Individual queries were clarified directly with the chief investigator with regular reviewing of progress. Further data-verification was taken during analysis stage with significant outliers, unexpected or improbable values and missing values queried and re-checked with the primary records by the relevant data-collector.

Patients were divided into two groups, therapeutic hypothermia (TH) and standard therapy (ST). The use of therapeutic hypothermia was defined *a priori* as documented active targeted temperature management to reduce to or maintain at a core temperature less than 35°C.

Data were collected using Utstein style recommended definition when available. Figure 7-1 show the data collection domains and time points. Demographic data included; age, weight, sex, presence of chronic conditions prior to OHCA and requirement for transportation to PICU. A chronic condition was defined as a pre-existing medical condition likely to increase risk of an OHCA. Aetiology of arrest was extrapolated from medical documentation using information until the time of discharge or from post-mortem reports if available. Categories included; pulmonary, cardiac, submersion (including near-drowning), neurological (non-traumatic), sepsis, inflicted traumatic brain injury, strangulation, near sudden infant death, trauma (including traumatic brain injury but excluding other injury related aetiologies already listed). Further comparative groupings of aetiology included asphyxial versus cardiac aetiology and non-traumatic versus traumatic (including all trauma aetiologies; submersion, strangulation, inflicted and non-inflicted traumatic brain, electrocution and 'other' trauma).

Cardiac arrest event characteristics were collected including: place of arrest, witnessed status, use of bystander cardiopulmonary resuscitation, first recorded rhythm on electrocardiograph (ECG) monitor by paramedic or emergency medicine staff, use and number of cardiac defibrillation attempts and doses of epinephrine. Date and time of

important key stages after OHCA were recorded as illustrated in Figure 7-2. Time intervals were calculated including duration of cardiac arrest (time of arrest to ROSC), duration of resuscitation from emergency department arrival to ROSC, time from ROSC to PICU admission and length of stay in PICU.

Physiological variables routinely available between ROSC and PICU admission were collected. Data was recorded whilst in the emergency department, during transportation or on arrival to PICU. Further data was collected at four hourly intervals after PICU admission.

Two sets of physiological data were analysed. First, maximum and minimum variables between ROSC and four hours post PICU admission were compared between TH and ST groups to identify differences in respect of covariates known to be associated with increased mortality (Chapter 6). Secondly, physiological variables were collected at 4 hourly intervals from PICU admission until 72 hours post admission (or death or PIC discharge, if earlier). These included; core temperature, heart rate, systolic blood pressure, mean blood pressure, partial pressure of oxygen (PaO_2) and carbon dioxide (PaCO_2) in the blood. These physiological variables were compared between two time periods: first 24 hours and 24-72 hours after PIC admission. The mean values for each variable was compared between the TH and ST groups. Heart rate and systolic blood pressure are presented in normalised units corrected for age using mean reference values (Elf et al, 2002).

Haematological values were compared including: haemoglobin, total white cell count, platelets, prothrombin time and activated partial thromboplastin time. The proportion with thrombocytopenia (platelet count less than $150 \times 10^9/\text{litre}$ of blood) was recorded. Biochemical values included sodium, potassium, magnesium, urea and creatinine levels.

Core temperature was collected, if recorded, at additional time points; at the time of OHCA, ROSC, admission to ED, leaving ED, admission to PICU and every four hours from PICU admission (defined as time zero) to 24 hours post admission. Core temperatures were defined as either rectal, oesophageal or bladder, as measured. Data were collected for all available temperature measurements. Episodes of excess hypothermia were defined as temperature less than 32°C and hyperthermia greater than 38°C on core temperatures.

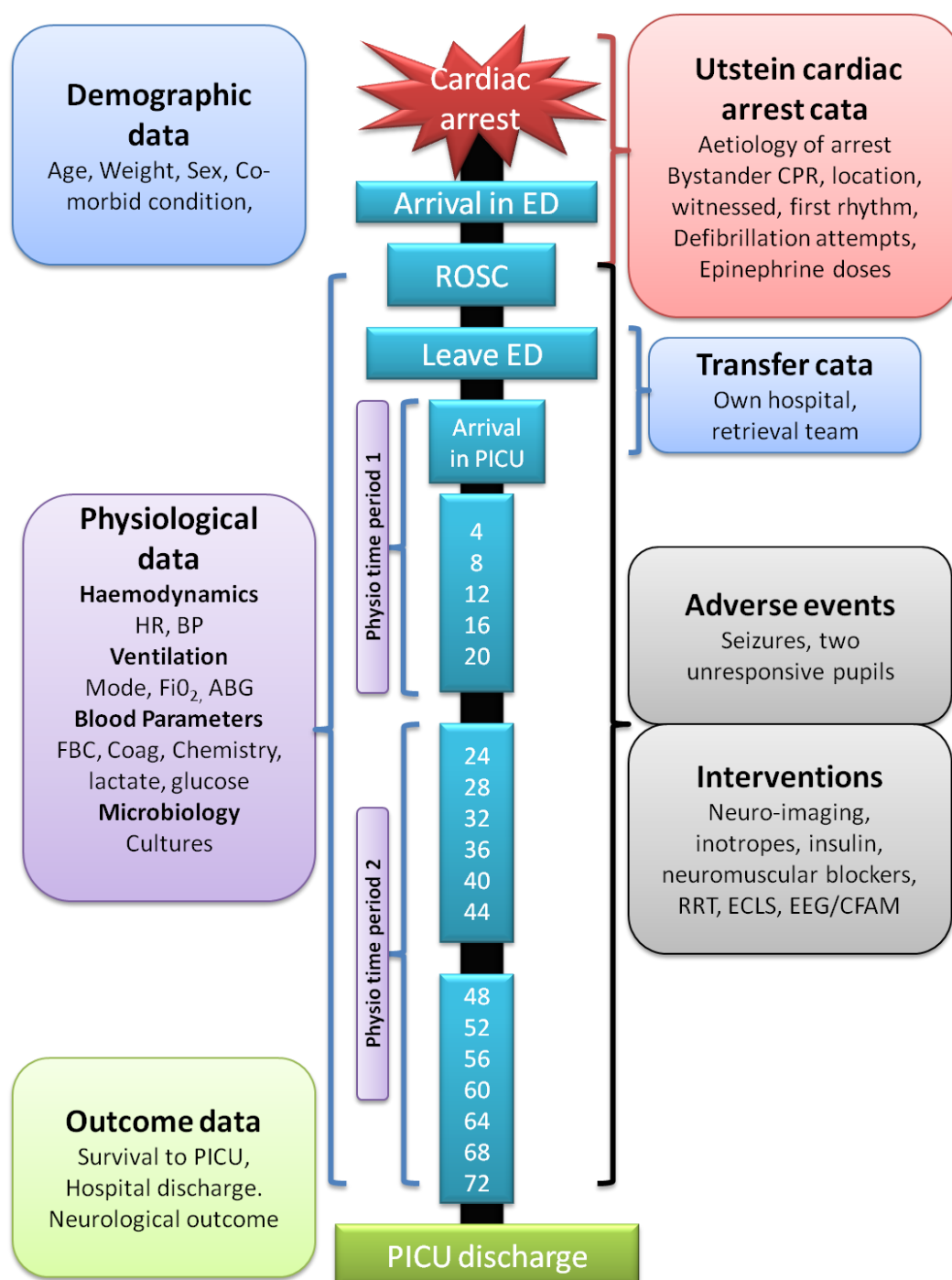
Key time points during the application of TH were identified through the review of patients' charts. These included, commencement of TH, reaching target temperature, commencement of rewarming and reaching final post-rewarming temperature (Figure 7-3). Duration of time and change in temperature was calculated between each time point.

Occurrence of seizures within the time period ROSC to 72 hours, presence of two unresponsive pupils at PICU admission and any major complication was also collected.

Post cardiac arrest treatments and investigations included; use and type of mechanical ventilation, inotropic support, extra-corporeal life support (ECLS), renal replacement therapy (including haemofiltration and peritoneal dialysis), insulin therapy, anti-seizure therapy, use and type of neuro-imaging and neuro-electrophysiological investigation.

The primary outcome was survival at hospital discharge. We also attempted to assess neurological outcome using the paediatric cerebral performance category (PCPC) score (Fiser et al, 2000) at PICU discharge and hospital discharge, calculated using information from the medical notes. However, the recording of information to guide category scoring was missing in up to 50% of survivors and therefore neurological outcome scoring could not be used in the current analysis.

Figure 7-1 Study Flow chart showing data collection areas at key time point.



HR: heart rate, BP: blood pressure (systolic and mean), Mode: conventional ventilation or high frequency oscillation, FiO₂, fractional inspired concentration of oxygen, ABG: arterial blood gas, FBC: full blood count, Chemistry: including urea, creatinine, and magnesium. RRT: renal replacement therapy, ECLS: extracorporeal life support, EEG/CFAM: electroencephalography and cerebral function monitoring.

Figure 7-2 Key time points for recording events and core temperature after OHCA

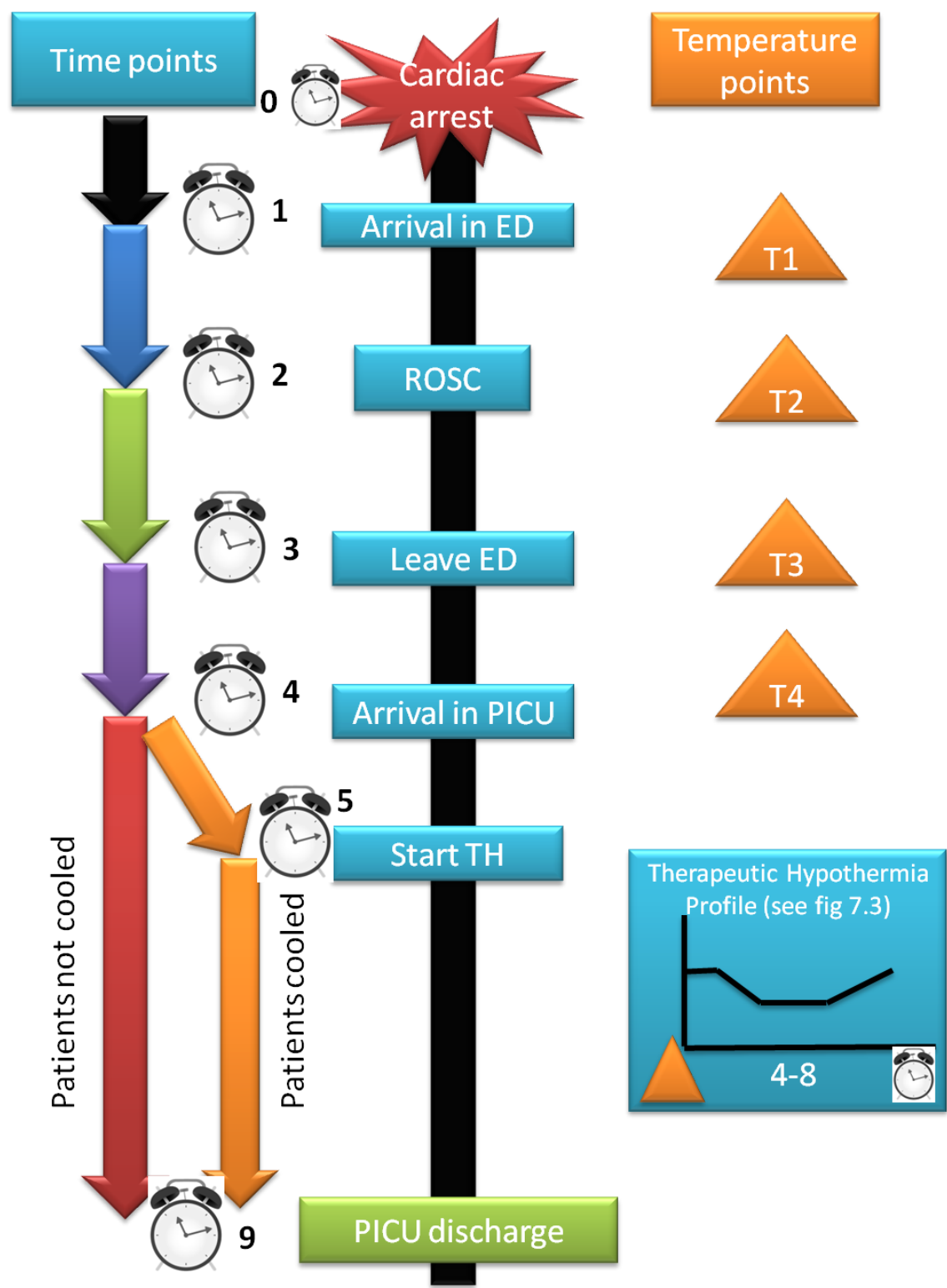
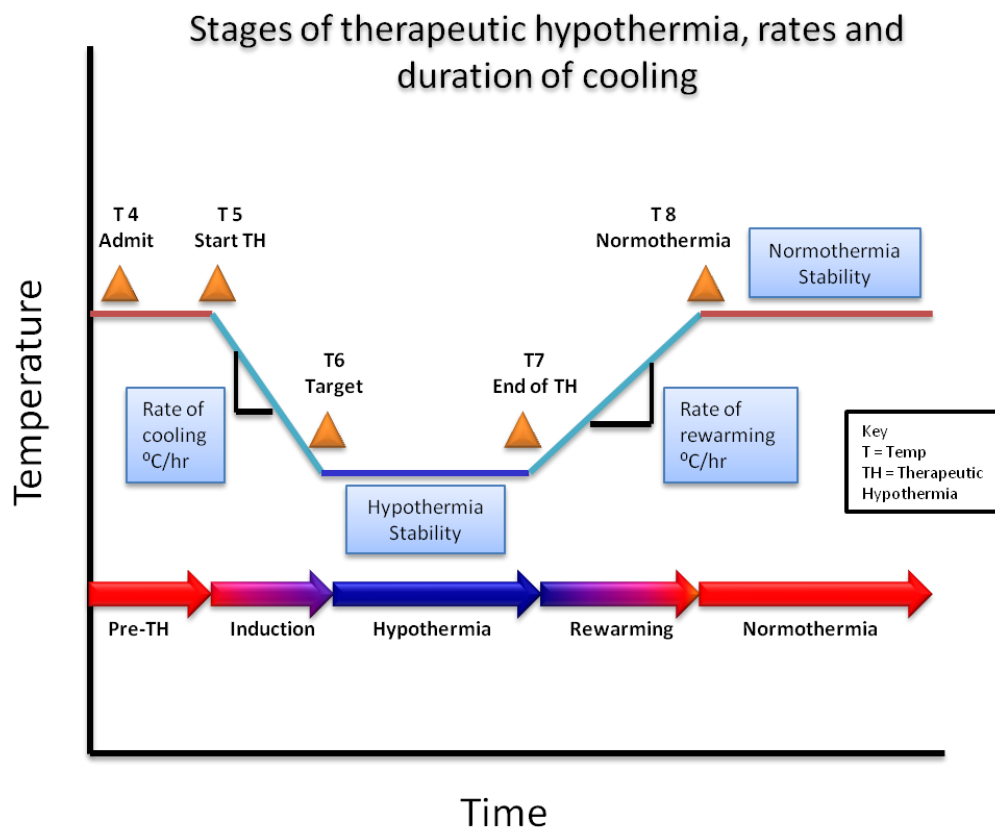


Figure 7-3 Stages of therapeutic hypothermia, rates and duration of therapy



7.4.4 Therapeutic hypothermia application

In 2007 the intensive care unit consultant team, after an evidence-based review, actively considered therapeutic hypothermia after out of hospital cardiac arrest at Birmingham Children's Hospital. The decision to commence therapy was made solely by the admitting paediatric intensive care consultant on a case by case basis. A formal protocol was not introduced until November 2009. However, accepted practice involved initiation of therapeutic hypothermia on the PICU with the use of servo-controlled water blanket cooling mattresses (Blanketroll II, Cincinnati Sub Zero, Ohio, USA) to rapidly induce therapeutic hypothermia to a temperature between 33 to 34°C for 24 hours followed by controlled rewarming, by 0.5°C every 2 hours, using the servo-controlled blanket, back to normothermia (37°C). Neuromuscular blocking drugs (e.g. Rocuronium) were used to prevent or treat shivering as well as receiving sedation and analgesia using intravenous morphine and midazolam. Patients were invasively ventilated with arterial blood gases monitored. PaCO₂ analysis was performed at 37°C and not adjusted for patient temperature (alpha-stat method) (Murkin, 2007). Standard neuroprotection PaCO₂ target range was 4.5 to 5.0kPa. Cardiovascular support in the form of inotropes was applied to maintain age appropriate blood pressure. Intracranial pressure monitoring was not used on this population. Clinical neurological assessment and additional neurological monitoring or imaging was performed if required; however, appropriate, active withdrawal of intensive care occurred following established UK guidelines which do not always require formal ancillary neurological assessment (RCPCH, 2004).

7.4.5 Statistical Analysis

We planned *a priori* for two separate analyses of the cohort to inform the feasibility of a randomised controlled trial. This chapter reports on the second analysis comparing patients receiving TH with those receiving ST to evaluate outcome and physiological differences between TH and ST.

Data were tested for normality by using the Shapiro-Wilk's W test. Descriptive data were reported as median and interquartile range (IQR) or mean \pm 95% confidence interval of the

mean for continuous variables and as frequencies and percentages for categorical variables. Parametric continuous data were analysed using the unpaired Student t-test and non-parametric continuous data with the Mann Whitney U test or Kruskal-Wallis, as appropriate. Categorical data were analysed using the Chi² or Fisher's exact tests, as appropriate.

A p value of <0.05 was considered statistically significant throughout. Data analyses were performed using either IBM-SPSS Statistics version 19.0 software (SPSS Inc, Chicago, USA) or Minitab 16 (USA).

7.5 RESULTS

7.5.1 Demographics

73 patients fulfilled the inclusion criteria (Figure 7-4). 38 (52%) received therapeutic hypothermia (TH) and 35 (48%) standard therapy (ST). Table 5-3 reports the demographic comparison of the two groups. There were no differences in age or weight in patients receiving either treatment. However, more males received TH ($p=0.049$). Overall 45% of patients had an underlying chronic condition. All chronic conditions were similar across the two groups except that no patient with a genetic condition (e.g. Down's syndrome) received TH ($p=0.048$). Half the patients required transportation from a secondary hospital. There was a significant increase in patients receiving TH over the seven year study period ($p<0.001$) (Figure 7-5).

Figure 7-4 Flow chart of included patients

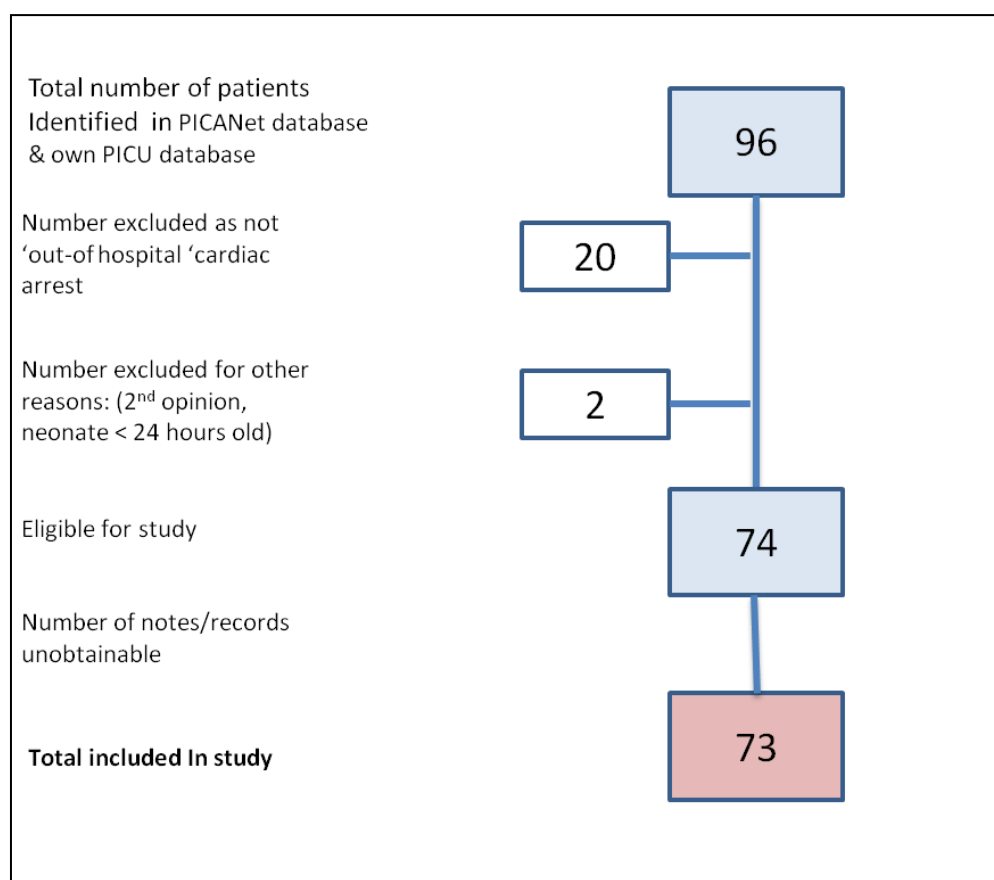


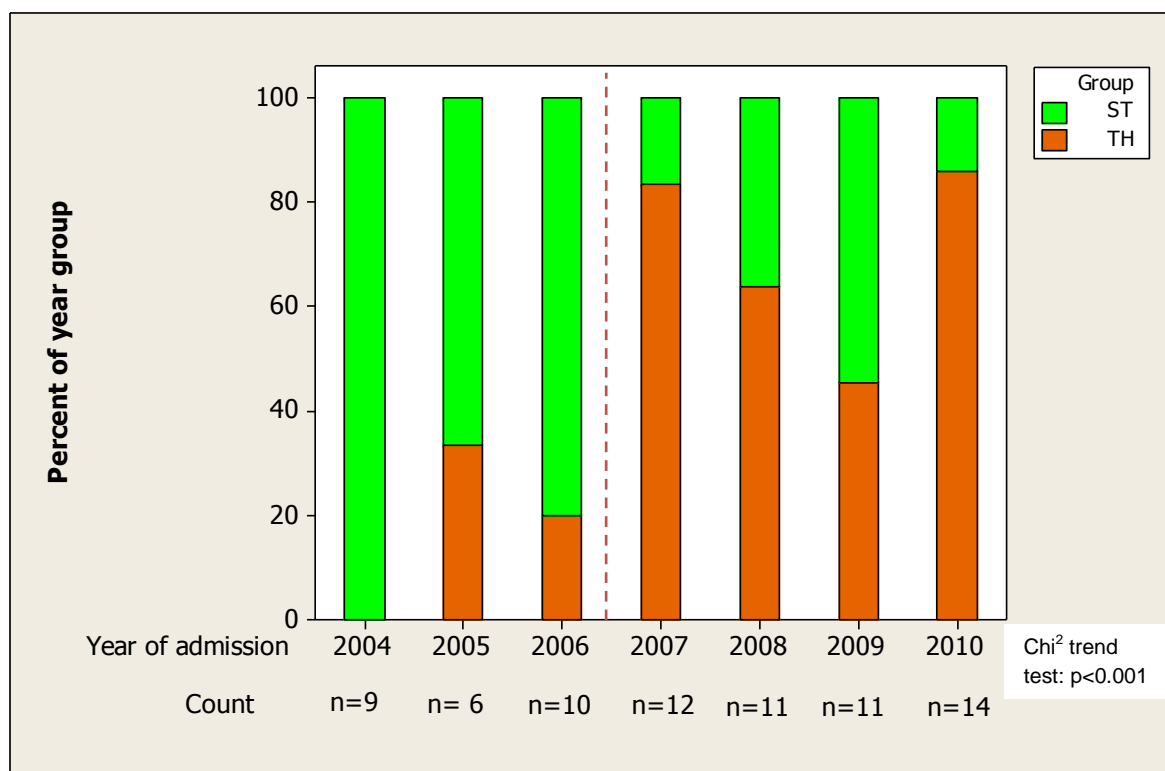
Table 7-1 Demographics and relationship to treatment groups

	Total Group n =73	TH n=38	ST n = 35	p ^b
Age (years)	1.0 (0-5.0)	1.5 (0-5.8)	1.0 (0-4.0)	0.735
Weight (kg)	8 (4-15)	10 (6-20)	6 (4-12)	0.061
Age category (Utstein ^a)				0.565
1-30 days	7 (10%)	5 (13%)	2 (6%)	
31 days to < 1 yr	23 (32%)	10 (26%)	13 (38%)	
1yr to < 4yrs	21 (29%)	11 (29%)	10 (29%)	
4yrs to < 12yrs	9 (13)	4 (11%)	5 (15%)	
12yrs to < 16yrs	12 (17%)	8 (21%)	4 (12%)	
Male	25 (34%)	17 (45%)	8 (23%)	0.049
Chronic Condition	33 (45%)	15 (39%)	18 (51%)	0.305
Two or more chronic conditions	14 (19%)	7 (18%)	7 (20%)	0.535
Neurological	17 (23%)	9 (24%)	8 (23%)	0.933
Respiratory	13 (18%)	7 (18%)	6 (17%)	0.887
Cardiac	4 (5%)	1 (3%)	3 (9%)	0.265
Prematurity	3 (4%)	1(3%)	2 (6%)	0.604
Genetic	5 (5%)	0	4 (12%)	0.048
Metabolic	4 (5%)	2 (4%)	2 (3%)	0.707
Gastrointestinal	1 (1%)	1 (3%)	0	1.0
Renal	1 (1%)	0	1 (3%)	1.0
Transported from different admitting hospital	37 (51%)	17 (45%)	18 (53%)	0.336

^a Utstein pre-defined age groups with modified upper age limit to less than 16 years (Zaritsky et al, 1995). Results expressed as Median (Inter-quartile range) or number (percent).

^b Chi² test or Fishers exact test was used for categorical variable and Mann Whitney U test for continuous variables.

Figure 7-5 Percentage of patients receiving therapeutic hypothermia



Dashed red line indicates first publication date of ILCOR guidelines for paediatric therapeutic hypothermia use: Published on-line April 17th 2006 - "Induction of hypothermia (32 to 34°C) for 12 to 24 hours should be considered in children who remain comatose after resuscitation from cardiac arrest." (ILCOR, 2006)

7.5.2 Aetiology

Therapeutic hypothermia was used more frequently in patients whose cause of arrest was unknown and less in patients presenting with cardiac arrest associated with accidental traumatic brain injury or other traumatic injury (Table 7-2).

Table 7-2 Aetiology of arrest and relationship to treatment groups

	Total Group n =73	TH n=38	ST n = 35	p^b
Not Known	12 (16%)	9 (23%)	3 (9%)	0.12
Pulmonary	16 (22%)	9 (24%)	7 (20%)	0.78
Cardiac	5 (7%)	4 (11%)	1 (3%)	0.19
Trauma (including accidental traumatic brain injury)	10 (14%)	2 (5%)	8 (23%)	0.04
Submersion	6 (8%)	3 (7%)	3 (9%)	1.0
Neurological	7 (10%)	2 (5%)	5 (14%)	0.25
Sepsis	5 (7%)	2 (5%)	3 (9%)	0.67
Inflicted traumatic brain injury	1 (1%)	1 (3%)	0	1.0
Strangulation	3 (4%)	2 (5%)	1 (3%)	1.0
(near) Sudden infant death syndrome	2 (3%)	0	2 (5%)	0.23
Other	6 (8%)	4 (11%)	2 (6%)	0.68

Results expressed as number (percent).

^b Fishers exact test was used for categorical variable

7.5.3 Cardiac arrest resuscitation factors and time data

Rates of OHCA occurring in the home or being witnessed were similar for patients receiving TH and ST (Table 7-3). However, patients receiving TH had significantly more reported episodes of bystander CPR. In all, six patients presented in a shockable rhythm (ventricular fibrillation or ventricular tachycardia) and 5 out of 6 received TH ($p=0.202$). The presenting rhythm was not known in 7 (10%) cases (3 received TH). Table 6-6 reports the time intervals for duration of cardiac arrest. Total CPR was similar for both groups although there was a trend towards an increased duration for children receiving TH (40 minutes versus 29 minutes). However, the median duration of CPR in the emergency department was similar (12 versus 13 minutes). An equally small proportion of patients (3% vs. 9%; $p=0.237$) had ROSC prior to arrival at the emergency department with a similar time from ROSC to final PICU admission for both group.

Table 7-3 Cardiac arrest resuscitation factors and relationship to treatment groups

Cardiac arrest resuscitation events	Total Group n =73	TH n=38	ST n = 35	p ^b	missing
Location own home (versus public place or other)	45 (68%)	23 (70%)	22 (67%)	0.792	7
Witnessed arrest	45 (65%)	23 (62%)	22 (69%)	0.567	4
Bystander CPR	45 (65%)	30 (81%)	15 (47%)	0.003	4
VF/VT ^a (vs. PEA/bradycardia/asystole)	6 (9%)	5 (14%)	1 (3%)	0.202	7
Pulseless electrical activity (PEA)	10 (15%)	6 (17%)	4 (13%)		
Bradycardia	7 (6%)	2 (6%)	5 (11%)		
Asystole	43 (65%)	22 (63%)	21 (67%)		
Ventricular fibrillation (VF)	5 (8%)	5 (14%)	0		
Pulseless Ventricular tachycardia (VT)	1 (2%)	0	1 (3%)		
Defibrillation attempted	10 (14%)	7 (18%)	3 (10%)	0.281	6
Epinephrine doses during resuscitation ^c		3 (1-4)	3 (1-4)	0.825	4
No epinephrine given during resuscitation	6 (9%)	2 (5%)	4 (13%)	0.401	4

CPR denotes cardiopulmonary resuscitation. ^aFirst recorded rhythm after cardiac arrest. VF: ventricular fibrillation, VT: ventricular tachycardia, PEA: pulseless electrical activity

^aUnavailable (missing) values were excluded from calculations of summary statistics. Results expressed as Median (Inter-quartile range) or number (percent).

^b Chi² test or Fishers exact test was used for categorical variable.

^c median value rounded up to nearest whole value, Mann Whitney U test used for continuous data.

Table 7-4 Time data and relationship to treatment groups

	Total Group n =73	TH n=38	ST n = 35	<i>p</i>^b	missing
Time duration from cardiac arrest onset to ROSC (mins)	38 (24-49)	40 (26-56)	29 (21-46)	0.226	5
ROSC prior to ED admission	8 (6%)	2 (3%)	6 (9%)	0.237	4
Time from ED admission to ROSC (mins)^a	12 (5-19)	12 (4-20)	13 (8-18)	0.979	4
Time duration from ROSC to PICU admission (hrs:mins)	02:57 (01:13-04:34)	02:50 (01:24-04:51)	03:20 (00:50-04:29)	0.666	5

ROSC denotes return of spontaneous circulation. ED: emergency department, PICU Paediatric intensive care unit. Unavailable (missing) values were excluded from calculations of summary statistics. Results expressed as Median (Inter-quartile range) or number (percent).

^a Only patients receiving CPR at ED admission were included in calculation

^b Chi² test was used for categorical variable and Mann Whitney U test for continuous variables.

7.5.4 Physiological variables

Using the physiological variables associated with worse outcome after OHCA (identified in chapter 6), a comparison between patients receiving TH and ST was performed (Table 6-7). Maximum and minimum lactate, pH, glucose, base deficit and the Paediatric Index of Mortality 2 (PIM2) score results were all similar between the two treatment groups. 11% (8/73) patients had documented seizures and 64% (41/64) had two unresponsive pupils on PICU admission with no differences noted between treatment groups (Table 6-8).

Table 7-5 Prognostic outcome variables (available between ROSC to four hours after PICU admission) and relationship to treatment groups

	Total Group n =73	TH n=38	ST n = 35	p^b	missing
Minimum pH	6.9 (6.7-7.2)	6.9 (6.7-7.2)	6.9 (6.7-7.2)	0.740	3
Maximum pH	7.3 (7.2-7.4)	7.3 (7.2-7.4)	7.3 (7.1-7.4)	0.249	3
Minimum lactate (mmol/l)	3.5 (2.2-8.3)	3.6 (2.4-7.8)	3.3 (1.9-9.8)	0.610	14
Maximum lactate (mmol/l)	5.4 (3.5-11.0)	6.3 (4.1-12.8)	4.2 (2.4-10.1)	0.158	14
Minimum glucose (mmol/l)	9.5 (5.9-12.8)	10.3 (6.2-12.3)	8.4 (4.6-13.6)	0.348	4
Maximum glucose (mmol/l)	15.5 (10.7-19.9)	15.8 (13.1-20.7)	14.4 (7.1-18.7)	0.076	4
Minimum base excess (mEq/l)	-19.6 (-24.7 to -13.1)	-19.9 (-25.4 to -13.0)	-18.1 (-24.4 to -12.9)	0.951	3
Probability of death by PIM2^a	0.84 (0.43-0.94)	0.91 (0.45-0.96)	0.81 (0.41-0.92)	0.151	3
Lactate > 3 mmol/l on PICU admission	43 (78%)	28 (80%)	15 (75%)	0.666	14

Values expressed as Median (interquartile range).

^a PIM2 (Paediatric index of mortality 2) (Slater et al, 2003) calculated on PICU admission data for all cases including patients transported by PICU specialist retrieval team

^b Unavailable (missing) values were excluded from calculations of summary statistics. Chi² test was used for categorical variable and Mann Whitney U test for continuous variables.

Table 7-6 Clinical neurological variables and relationship to treatment group

	Total Group n =73	TH n=38	ST n = 35	p^b	Missing
Seizures	8 (11%)	3 (8%)	5 (14%)	0.470	2
Two unresponsive pupils	41 (64%)	21 (58%)	20 (71%)	0.279	9

Values expressed as numbers (percent of total group, survivors or nonsurvivors). Chi² test was used for categorical variable

7.5.5 Core Temperature in Emergency Department and PIC admission

Temperature at arrival to the emergency department, ROSC, and leaving the emergency department, were similar for patients subsequently receiving TH or ST in the PICU. Table 7-7 show comparable temperatures and highlights the high number of missing values at each time point. Overall, in the emergency department, 30% (22/73) had no record of temperature measurement.

All patients had a temperature at admission to PICU recorded (Table 7-8). Patients receiving TH were significantly cooler (34.3°C vs. 36.1°C; $P=0.007$). Incorporating all temperatures from ED admission to four hours post PIC admission (used in the predictive models in Chapter 6), patients receiving TH had significantly lower minimum and maximum temperatures.

In a subgroup analysis of TH patients only, admission to PICU temperature was higher in survivors (35.4 (IQR [34.0 to 36.3])°C) versus non survivors (34.0 (IQR [32.6 to 35.6])°C) although this did not reach statistical difference ($p=0.140$).

Figure 7-6 illustrates the temperature profile of patients receiving TH and ST. There continued to be a significant difference in temperature between the two groups from PIC admission up to 40 hours after admission.

Five (7%) patients in the study presented at the ED with temperatures less than 30°C, of these patients, one received TH and four ST.

Four patients who received TH and two who received ST experienced severe hypothermia (temperature <32°C) after arrival to PIC (Table 7-9). All eleven patients, with any recorded temperature <32°C from ED admission to 24 hours post PIC admission, died prior to PIC discharge.

Hyperthermia (temperature >38°C) in the first 24 hours after PIC admission was significantly reduced in patients receiving TH (1/35; 3%) versus ST (12/32; 38%, $p<0.001$).

Table 7-7 Core temperature measurement in the emergency department (ED) in relationship to treatment groups

Core temperature (°C)	Total Group n = 73	TH n=38	ST n = 35	<i>p</i> ^b	Missing value
Temperature at arrival to ED	34.8 (33.7-36.0)	34.3 (34.0-35.3)	33.9 (30.7-35.3)	0.434	45
Temperature at ROSC	34.1 (33.0-35.1)	34.1 (33.7-35.1)	34.1 (32.8-35.2)	0.753	33
Temperature leaving ED	34.8 (33.7-36.0)	35.0 (33.5-36.1)	34.5 (33.9-36.0)	0.929	42
Minimum temperature recorded in ED	34.1 (33-35.1)	34.1 (33.9-35.1)	33.3 (31.5-35.2)	0.160	22
Maximum temperature recorded in ED	35.2 (34.1-36.0)	35.3 (34.1-36.1)	35.2 (34.2-36.0)	0.559	22

Numbers expressed as Median (interquartile range). Mann Whitney U test was used for continuous variables. ^b Unavailable (missing) values were excluded from calculations of summary statistics.

Table 7-8 Core temperature measurements at PICU admission and relationship to treatment groups

Core temperature (°C)	Total Group n = 73	TH n=38	ST n = 35	<i>p</i> ^b	Missing value
Temperature at PICU admission	35.2 (33.5-36.5)	34.3 (32.8-35.9)	36.1 (34.0-37.0)	0.007	9
Minimum temperature after ROSC To 4hrs post PICU admission	33.5 (32.5-34.8)	33.1 (32.5-34.1)	34.1 (32.5-36.0)	0.068	4
Maximum temperature after ROSC To 4hrs post PICU admission	36 (34.9-37.0)	35.8 (34.5-36.5)	36.5 (35.5-37.2)	0.014	4

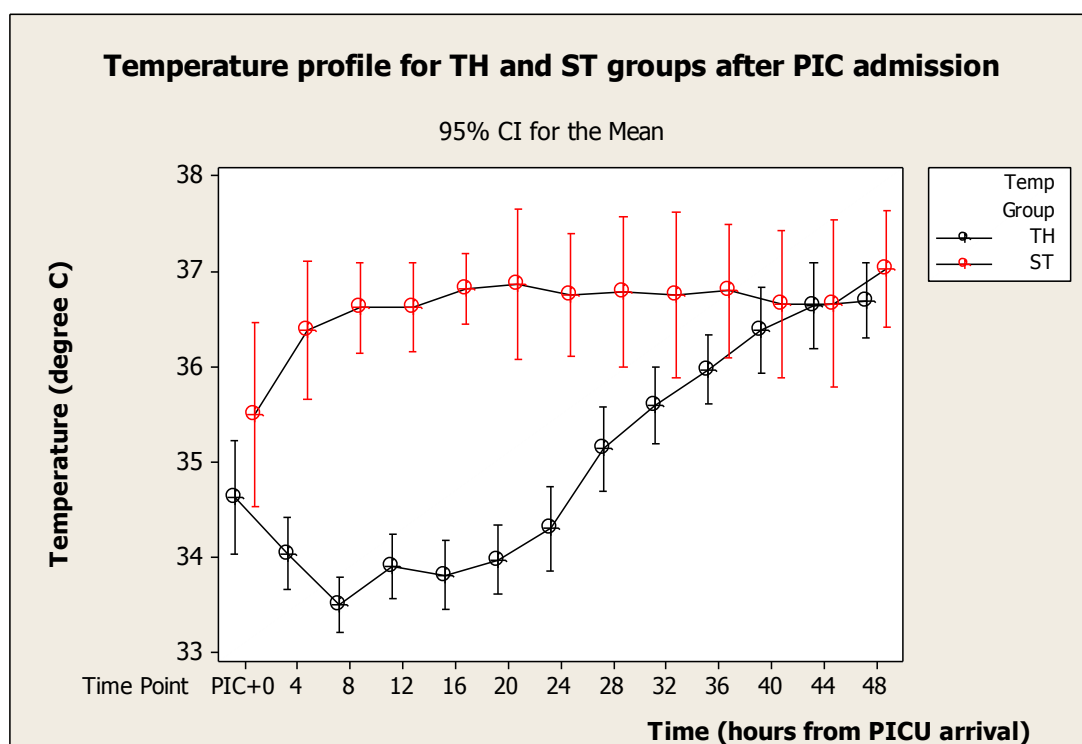
Numbers expressed as Median (interquartile range). Mann Whitney U test was used for continuous variables. ^b Unavailable (missing) values were excluded from calculations of summary statistics.

Table 7-9 Relationship of severe hypothermia (<32°C) or hyperthermia (>38°C) to treatment groups

	Total Group n = 73	TH n = 38	ST n = 35	<i>p</i> ^b	Missing value
Any temperature <32°C ROSC to 24hrs post PICU admission	11 (16%)	5 (13%)	6 (19%)	0.525	4
Any temperature >38°C ROSC to 24hrs post PICU admission	13 (18%)	1 (3%)	12 (34%)	<0.001	4

^b Unavailable (missing) values were excluded from calculations of summary statistics. Chi² test or Fishers Exact test were used for categorical variable

Figure 7-6 Temperature profile of patients receiving therapeutic hypothermia and standard therapy

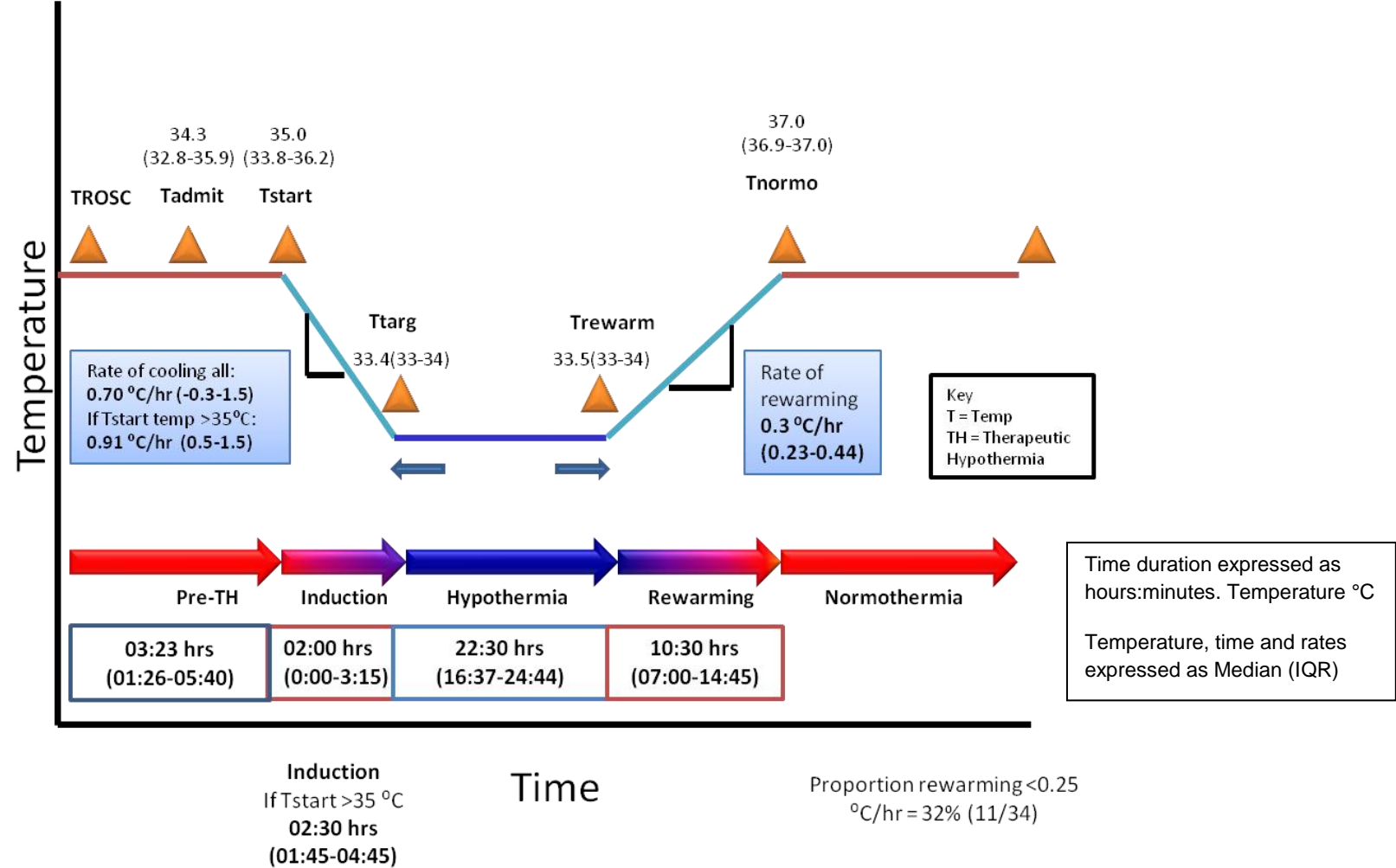


Mean temperature (with 95% confidence intervals for the mean). TH: therapeutic hypothermia, ST: standard therapy.

7.5.6 Application of therapeutic hypothermia

Thirty eight patients received TH. Figure 7-7 illustrates specific details of timing, temperatures and rates of induction and rewarming of the therapy for the TH group. Median temperature at the start of TH was 35.0 (IQR [33.8 to 36.2])°C. In the 50% of patients with a temperature >35°C at the start of TH, induction of temperature to target temperature occurred at a rate of 0.91 (IQR [0.5 to 1.5]) °C/hr. Four patients (11%) had overshoot hypothermia (<32°C) following induction. Median target temperature was 33.4°C and was maintained for a median of 22:30 (IQR [16:37 to 24:44]) hours:minutes. Rewarming occurred over a median of 10:30 (IQR [07:00 to 14:45]) hours:minutes at a rate of 0.3 (IQR [0.23 to 0.44])°C/hr. Three patients receiving TH died prior to rewarming. Only 32% (11/34) rewarmed slower than or equal to 0.25°C/hr. Hyperthermia (>38°C) after rewarming occurred in 29% (10/34).

Figure 7-7 Stages of therapeutic hypothermia, temperatures, rates and duration of cooling (n=38)



7.5.7 Physiological effects of therapeutic hypothermia in comparison to standard therapy

Comparison of the TH and ST groups with regards physiological, haematological, biochemical and acid base parameters are presented in Table 7-10, Table 7-11, Table 7-12 and Table 7-13 respectively.

Overall, measured heart rate was lower in the TH compared with the ST group during the first 24 hours after ROSC ($p=0.003$). However, after normalisation for age (see methods section) this difference was no longer statistically significant ($p=0.147$). Systolic, normalised systolic and mean blood pressures were also similar between TH and ST groups (Figure 7-8).

Bradycardia (defined as $<10^{\text{th}}$ centile for age) and extreme bradycardia ($<1^{\text{st}}$ centile age) occurred in twice as many patients treated with TH compared to ST. 42% (16/38) of TH patients had an episode where heart rate fell below 10^{th} centile for age compared to 19% (6/32) in the ST group (Fisher exact test $p=0.04$). Episode of extreme bradycardia ($<1^{\text{st}}$ centile age) occurred in 21% (8/28) of TH patients versus 10% (3/30) of ST although this difference did not reach statistical significance ($p=0.208$).

Arterial oxygen content (PaO_2) was significantly higher during the first 24 hours in both groups compared to 28-72 hours. However, no difference was noted between TH and ST groups.

Arterial carbon dioxide content (PaCO_2) was similar between TH and ST groups; however, nearly half of patients in both groups experienced severe hypocarbia ($\text{PaCO}_2 < 4.0\text{kPa}$) during the first 24 hours after ROSC (TH: 16/38 (42%) vs. ST: 14/30 (47%) $p=0.707$). This proportion reduced during the subsequent 48 hours in both groups (TH: 7/35 (20%) vs. ST: 2/15 (13%) $p=0.705$).

Only white cell count, during 0-24 hours post ROSC, differed between TH and ST groups. All other haematological values were similar. 25% (9/35) of TH patients and 32% (10/31) of ST patients developed thrombocytopenia during 0-24 hours

($p=0.511$). This increased to 34% (12/35) and 58% (7/12) during the stage 25-72 hours after ROSC ($p=0.182$). Although data was missing after 25 hours in 23/35 ST patients due to death or hospital discharge.

Sodium levels in TH patients were statistically significantly higher in TH compared to ST patients 0-24 hours after ROSC ($p=0.011$). However, this only reflected a 3mmol/L increment in measured plasma sodium and therefore unlikely to be a clinically significant difference. Magnesium levels were similar between TH and ST; however significantly reduced in both groups by 24-72 hours post PIC admission. All other biochemical variable measures were similar for TH and ST patients and did not significantly change between 0-24 hours and 25-72 hours (Figure 7-9).

There was no difference in pH, base excess, lactate and glucose between TH and ST groups. All four parameters improved towards normal limits for both groups by 25-72 hours (Figure 7-10).

Table 7-10 Cardiovascular and respiratory variables

	0-24 hours			25-72 hours		
	TH n=38	ST n = 35	<i>p</i> ^b	TH n=38	ST n = 35	<i>p</i> ^b
Heart Rate (beat per minute)	134 (114-142)	148 (127-166)	0.003	140 (123-145)	144 (123-150)	0.476
Normalised HR	1.02 (0.95-1.71)	1.20 (1.02-1.37)	0.147	1.18 (0.95-1.38)	1.16 (1.06-1.44)	0.739
Systolic BP (mmHg)	102 (83-117)	96 (85-114)	0.563	100 (86-110)	98 (82-117)	0.736
Normalised Systolic BP	1.11 (0.96-1.22)	1.15 (0.90-1.28)	0.697	1.07 (0.99 (1.16)	1.20 (1.00-1.39)	0.115
Mean BP (mmHg)	73 (60-85)	74 (60-83)	0.715	74 (65-81)	70 (62-85)	0.878
PaO₂ (kPa)	14.6 (10.6-19.5)	17.5 (11.0-21.9)	0.475	11.8 (10.0-13.3)	10.3 (9.2-15.5)	0.743
PaCO₂ (kPa)	6.1 (4.9-8.5)	6.5 (4.5-8.3)	0.743	4.9 (4.7-6.0)	5.1 (4.6-6.1)	0.966

Missing values for 3 patients all ST group; 0 to 24 hours. Missing values for 29 patients (6 TH and 23 ST group); 25 to 72 hours. Values expressed as Median (interquartile range). ^b Mann Whitney U test for comparison between TH and ST groups. Normalised to age specific reference range (Elf et al, 2002).

Table 7-11 Haematological variables

	0-24 hours			25-72 hours		
	TH n=38	ST n = 35	<i>p</i> ^b	TH n=38	ST n = 35	<i>p</i> ^b
Haemoglobin (g/dL)	11.7 (9.8-13.6)	11.5 (9.6-12.8)	0.266	11.0 (10.1-12.0)	10.6 (0.8-11.2)	0.335
White cell count (x10 ⁹ /L)	9.7 (7.1-14.0)	15.3 (7.3-20.7)	0.031	8.5 (5.2-13.0)	10.6 (6.8-14.9)	0.306
Platelets (x10 ⁹ /L)	244 (188-337)	262 (154-417)	0.852	195 (147-234)	159 (90-352)	0.542
Prothrombin time (seconds)	14.0 (12.5-5.3)	14.5 (13.0-6.0)	0.386	13.8 (12.9-16.0)	12.0 (11.5-9.0)	0.443
Activated partial thromboplastin time (seconds)	33 (28-41)	33 (29-41)	0.862	22 (28-36)	28 (26-33)	0.030

Missing values for 6 patients (2 TH and 4 ST; 0 to 24 hours). Missing values for 26 patients (3 TH and 23 ST group); 25 to 72 hours. Median (interquartile range). ^b Mann Whitney U test for comparison between TH and ST groups.

Table 7-12 Biochemical variables

	0-24 hours			25-72 hours		
	TH n=38	ST n = 35	<i>p</i> ^b	TH n=38	ST n = 35	<i>p</i> ^b
Sodium (mmol/L)	143 (140-144)	140 (136-142)	0.011	143 (139-147)	143 (138-146)	0.604
Potassium (mmol/L)	3.7 (3.3-4.3)	4.0 (3.5-4.7)	0.086	3.9 (3.8-4.4)	3.9 (3.6-4.3)	0.966
Urea (mmol/L)	5.5 (4.4-8.8)	5.8 (3.9-10.2)	0.510	6.1 (3.9-11.9)	5.3 (2.6-10.0)	0.257
Creatinine (μmol/L)	59 (39-81)	52 (39-70)	0.667	47 (39-84)	45 (30-54)	0.376
Magnesium (mmol/L)	0.98 (0.83-1.13)	0.90 (0.81-1.14)	0.438	0.81 (0.75-0.88)	0.77 (0.71-0.88)	0.563

Missing values for 12 patients (1 TH and 11 ST); 0 to 24 hours. Missing values for 32 patients (7 TH and 25 ST group); 25 to 72 hours. Median (interquartile range).^b
Mann Whitney U test for comparison between TH and ST groups.

Table 7-13 Blood gas parameters & Plasma glucose

	0-24 hours			25-72 hours		
	TH n=38	ST n = 35	<i>p</i> ^b	TH n=38	ST n = 35	<i>p</i> ^b
pH	7.21 (7.13-7.31)	7.21 (7.10-7.32)	0.664	7.35 (7.29-7.40)	7.36 (7.30-7.37)	0.958
Base Excess (mEq/L)	-10.8 (-13.7 to -7.4)	-9.6 (-12.6 to -6.0)	0.305	-5.6 (-7.0 to -3.1)	-4.2 (-7.0 to -1.35)	0.427
Lactate (mmol/L)	4.6 (2.8-7.5)	4.5 (2.6-9.1)	0.918	1.7 (1.1-2.9)	1.7 (1.3-2.1)	0.842
Glucose (mmol/L)	11.3 (9.3-12.9)	9.6 (6.3-12.6)	0.129	6.1 (5.1-8.2)	6.0 (5.5-7.3)	0.735

Missing values for 4 patients all ST group; 0 to 24 hours. Missing values for 23 patients (3 TH and 20 ST group); 25 to 72 hours. Median (interquartile range).^b
Mann Whitney U test for comparison between TH and ST groups.

Figure 7-8 Physiological parameters comparing TH and ST at 0-24 hours and 25-72 hours

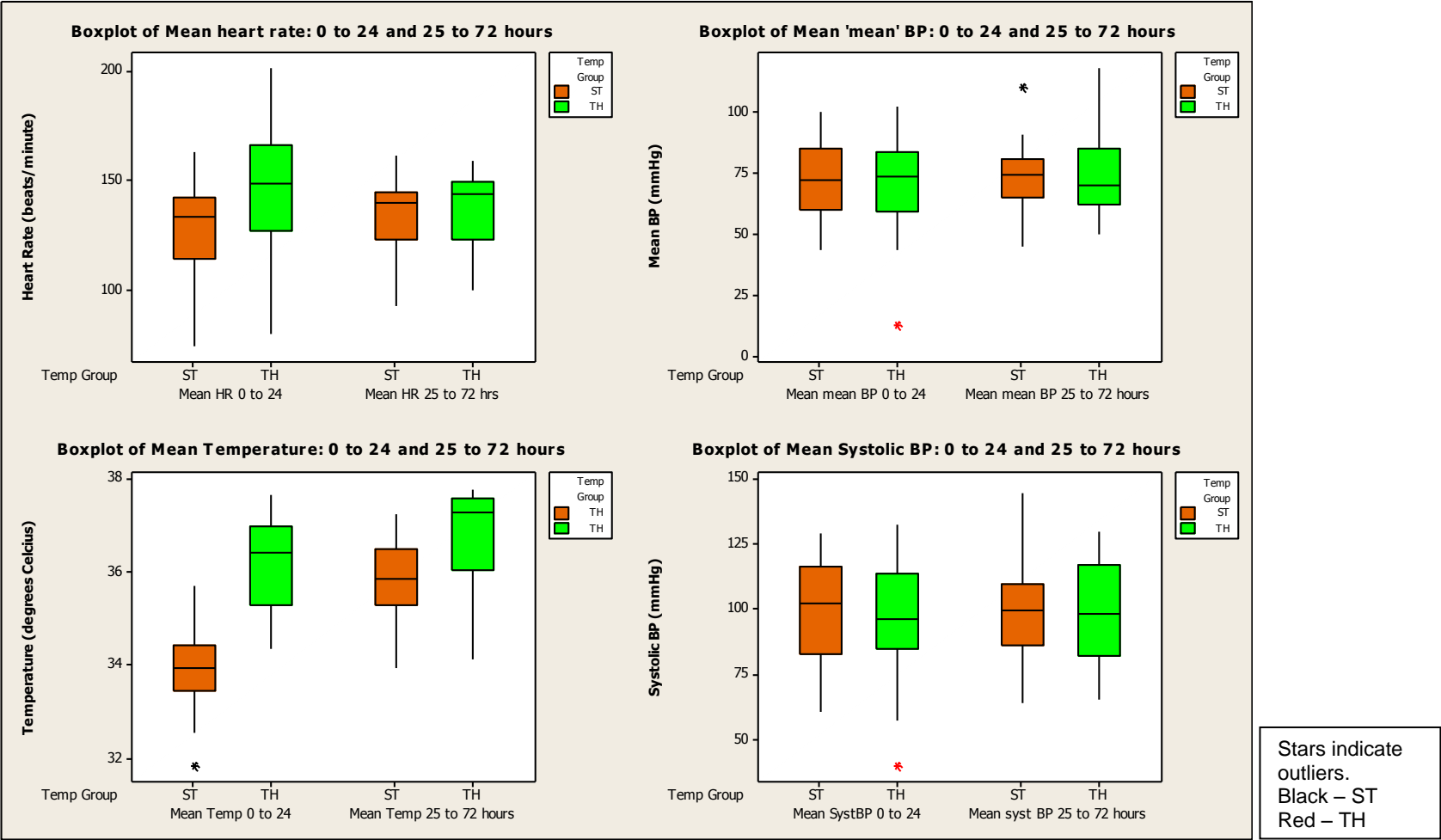


Figure 7-9 Biochemical variables comparing TH and ST at 0-24 hours and 25-72 hours

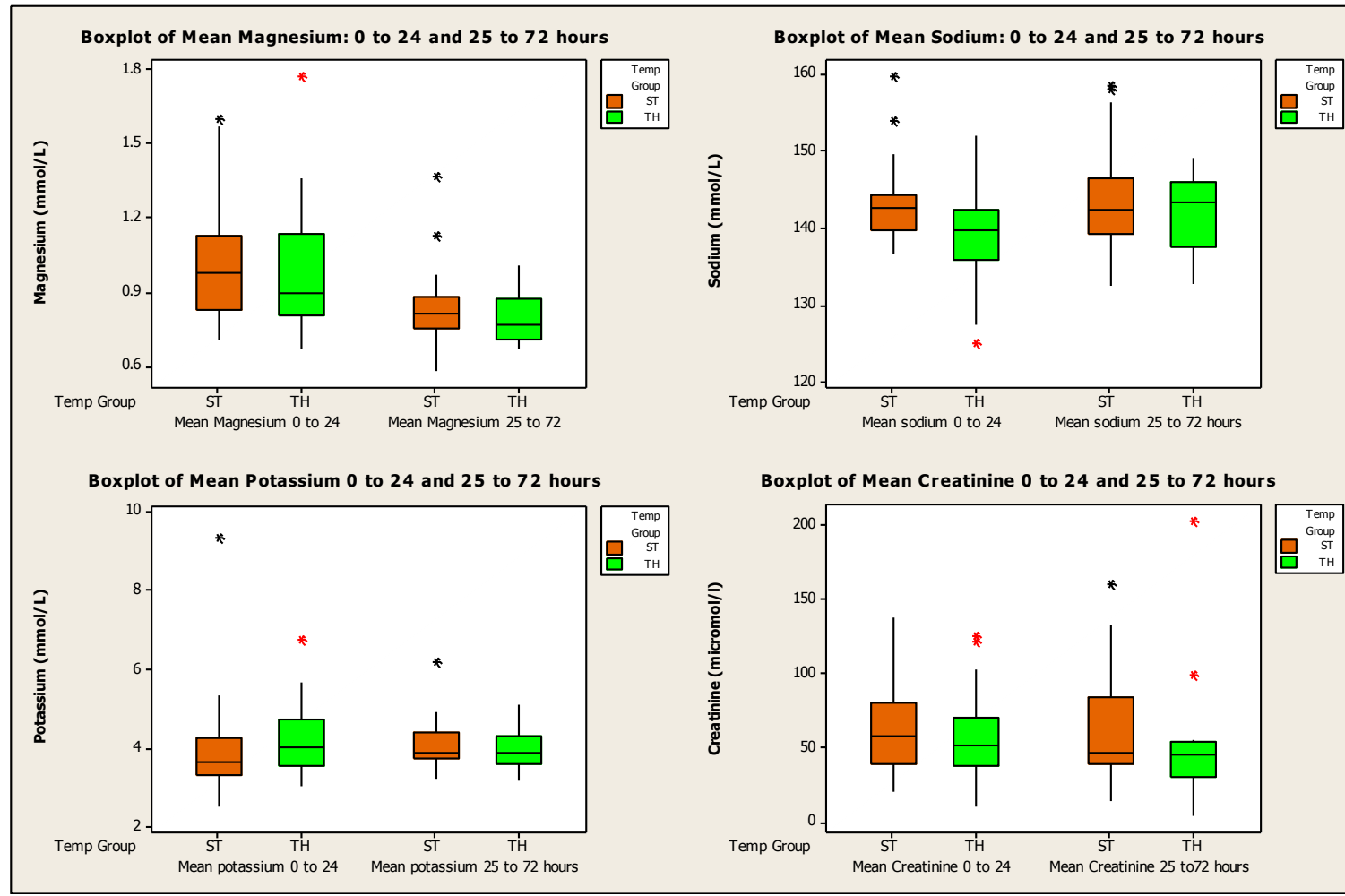
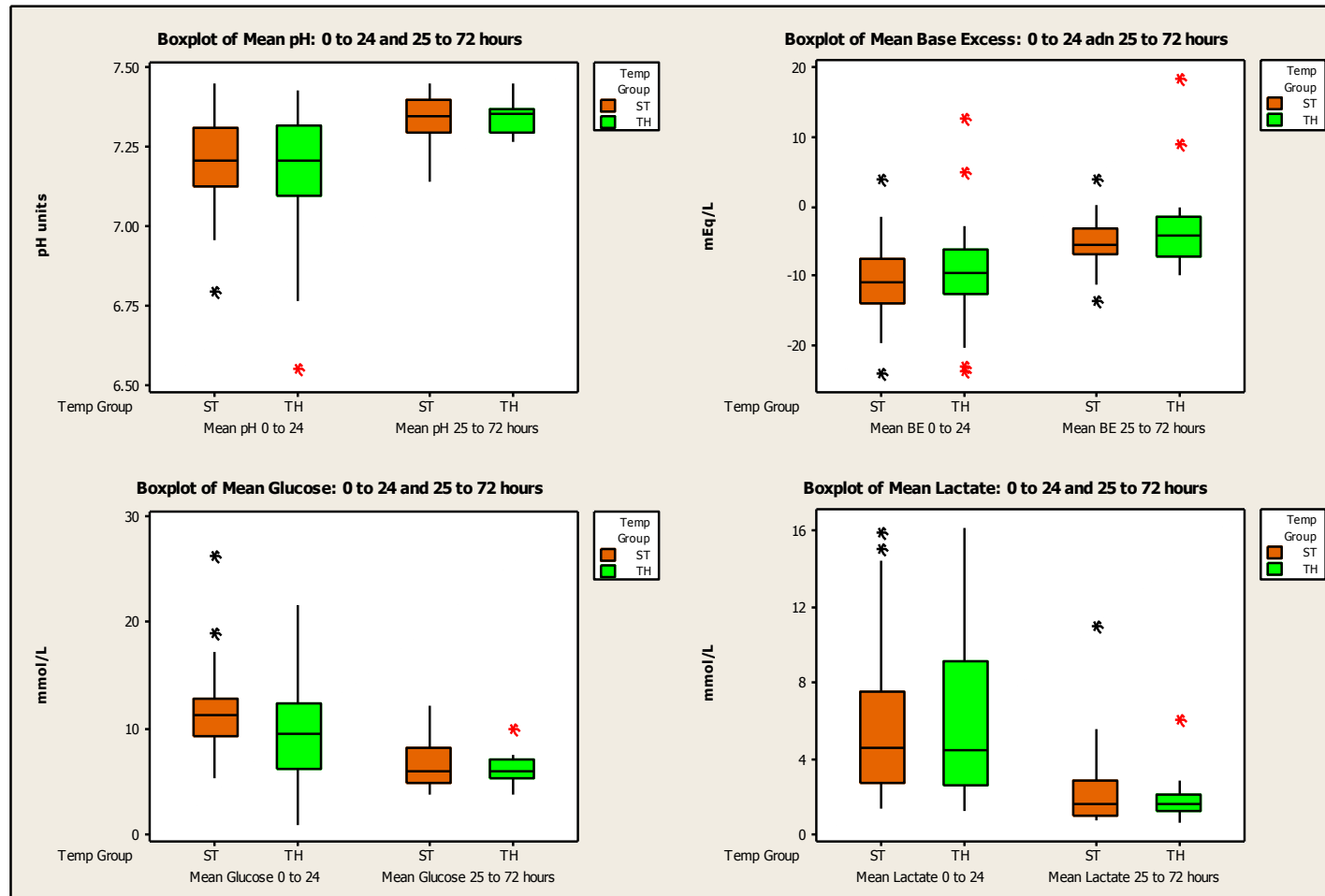


Figure 7-10 Acid base parameters comparing TH and ST at 0-24 hours and 25-72 hours



7.5.8 Additional PICU treatment interventions

All patients received mechanical ventilation. More patients receiving TH required inotropic support compared to ST, although the difference in proportions was not statistically significant. Only one patient in the TH group received extra corporeal life support (ECLS) for refractory cardiac arrest and rewarming due to profound hypothermia on admission (admission core temperature 14°C). No patients received renal replacement therapy. Insulin therapy was more frequent in the TH group (34% vs. 17%; $p=0.10$), although not reaching statistical significance.

MRI and EEG investigations were more common in the TH group, although a greater number of MRIs (71%; 17/24) and EEGs (89%; 17/19) were performed after 2007 and may also reflect a change in post cardiac arrest management during this later time period.

Table 7-14 Post arrest treatment & Investigational data in relationship to treatment group

	Total Group n =73	TH n=38	ST n = 35	p^b
Treatment				
Mechanical ventilation	73	38 (100%)	35 (100%)	1.0
Inotropes after resuscitation	47 (64%)	28 (74%)	19 (54%)	0.084
Two or more inotropes	11 (15%)	8 (21%)	3 (9%)	0.19
HFOV	2 (3%)	2 (3%)	2 (3%)	1.0
ECMO	1 (1%)	1 (3%)	0	1.0
Renal replacement therapy	0	0	0	
Insulin therapy	19 (26%)	13 (34%)	6 (17%)	0.097
Neuromuscular blockade after PICU admission	31 (42%)	16 (42%)	15 (43%)	0.948
Anti-seizure therapy	10 (14%)	6 (16%)	4 (11%)	0.74
Investigation				
Any neuroradiology	44 (60%)	26 (68%)	18 (51%)	0.138
MRI scan	24 (33%)	18 (47%)	6 (17%)	0.007
CT scan	30 (41%)	15 (39%)	15 (43%)	0.796
Any neuroelectrophysiology investigation^c	19 (26%)	15 (39%)	4 (11%)	0.008

^bChi² test was used for categorical. ^cIncludes: Electroencephalogram (EEG) and continuous amplitude integrated EEG

MRI: magnetic resonance imaging, CT: Computer tomography

7.5.9 Outcome

Table 7-15 reports outcome for patients receiving TH and ST. Overall survival to hospital discharge of patients admitted to PIC after OHCA was 29% (21/73). Survival to hospital discharge was 11% higher after TH compared to ST (34% vs. 23%), a relative risk increase of 48%; however, this difference did not reach statistical significance ($p=0.284$).

Overall, patients receiving TH stayed in PIC longer compared to ST (Median 4.1 (IQR [3.0 to 6.8] days vs. 1.3 (IQR [0.5 to 6.7]) days; $p < 0.001$) respectively. Although this difference was accounted for by patients who died in PIC (TH: 4.1 (IQR [2.6 to 5.2]) days vs. ST: 1.2 (IQR [0.4 to 2.4]) days; $p < 0.001$). Survivors receiving TH or ST had a similar length of stay in PIC (6.2 (IQR [3.0 to 7.8]) days vs. 6.7 (IQR [0.9 to 8.1]) days; $p=0.805$) respectively. There were also a similar proportion of patients in both groups who had withdrawal of life sustaining intensive care support prior to death. All (24/24) patients who died in PIC after receiving TH and 81% (22/27) after receiving ST had active withdrawal of intensive care support.

Neurological outcome scoring by PCPC for survivors was unfortunately missing in a large number of cases of hospital survivors (45%; 10/22). In the cases with known PCPC scores, two patients who received TH and two ST had a bad neurological outcome (PCPC score 3 to 4).

Table 7-15 Survival outcomes in relationship to treatment groups

	Total Group n =73	TH n=38	ST n = 35	<i>p</i> ^b
Outcome				
Survival to PICU discharge	22 (30%)	14 (37%)	8 (23%)	0.193
Survival to Hospital discharge	21 (29%)	13 (34%)	8 (23%)	0.284
PICU Length of stay (LOS) (days)	3.1 (1.3-6.6)	4.1 (3.0-6.8)	1.3 (0.5-6.7)	<0.001
PICU LOS for survivors (days)	6.5 (2.9-7.6)	6.2 (3.0-7.8)	6.7 (0.9-8.1)	0.805
PICU LOS for non-survivors (days)	2.4 (0.8-4.7)	4.1 (2.6-5.2)	1.2 (0.4-2.4)	<0.001
Withdrawal of intensive care support (proportion of patients who died in PICU)	46 (90%)	24 (100%)	22 (81%)	0.312
Fulfilled brain death criteria (proportion of patients who died in PICU)	9 (18)	5 (21%)	4 (15%)	0.730

LOS: length of stay ^bChi² test was used for categorical variable and Mann Whitney U test for continuous variables.

7.6 DISCUSSION

This is the largest study to date comparing the effects of therapeutic hypothermia (TH) and standard therapy (ST) in children after out-of-hospital cardiac arrest (OHCA). TH was used in 52% (38/73) of patients and did not result in a statistically significant improvement in hospital survival compared to ST (34% versus 23%; $p=0.284$).

Confounding factors known to influence survival, identified in Chapter 6, were equally balanced between patients in the TH and ST group. The only recorded differences at resuscitation and PIC admission between TH and ST patients were an increased incidence of bystander CPR and a non-significant trend towards increased duration of cardiac arrest in the TH group. This is in contrast to two previous paediatric observational studies. Doherty et al (2009) compared patients receiving TH ($n=29$) with normothermia ($n=50$). They reported an increased use of TH after, predominately, in-hospital cardiac arrest and in patients with a much higher predicted risk of mortality (longer duration of arrest, use of extracorporeal life support and increased propensity score). The use of TH was associated with a worse six month mortality outcome (unadjusted odds ratio (OR) 3.62 (1.37-9.62; $p=0.009$) and poorer neurological outcome (unadjusted OR 2.92 (1.1-7.69; $p=0.031$) after paediatric cardiac arrest. After adjustment, however, neither mortality nor neurological outcomes were different between patients receiving hypothermia and normothermia. Fink et al (2010) compared 40 children receiving TH compared with 141 receiving ST. Fifty one percent were after OHCA, 91% asphyxial arrests and excluded all children with congenital cardiac disease. Patients receiving TH had longer cardiac arrest duration and higher admission lactate levels. Overall the survival to hospital discharge was the same between patients receiving TH (45%) and ST (45%; $p=1.0$) with similar neurological outcome as assessed by the Glasgow Outcome Score (2.4 vs. 2.4; $p=0.9$).

Our study, in agreement with these two other paediatric retrospective studies, failed to demonstrate a statistically significant increase in survival. However, this is the first paediatric observational study with balanced treatment groups where a signal towards improvement is demonstrated by an 11% absolute risk increase (48% relative risk increase) in hospital survival.

7.6.1 Aetiology – Trauma

Therapeutic hypothermia was used less frequently in OHCA associated with trauma, including accidental traumatic brain injury. This is likely to reflect the decreased use of TH in all paediatric traumatic brain injury patients since the publication of the large RCT of TH versus normothermia after paediatric TBI in 2008 (Hutchison et al, 2008). Prior to this study, animal (Clifton et al, 1991) and small human studies (Adelson et al, 2005) suggested that TH may improve neurological outcome and survival after TBI. However, in this study, TH did not improve good neurological outcome (relative risk, 1.41 (95% confidence interval [CI], [0.89 to 2.22]); $p=0.14$) and showed a trend towards increased mortality (relative risk, 1.40 (95% CI [0.90 to 2.27]); $P=0.06$). A large adult RCT of TH after TBI also reported a lack of benefit with TH treatment (Clifton et al, 2001). The complex pathophysiological interplay of hypoxic ischaemic and traumatic injury to the brain in these patients will be very difficult to separate in clinical trials of heterogeneous populations. Continued assessment of clinical benefit of TH in separate populations will be important before focusing on this small but important subpopulation.

7.6.2 Aetiology – Drowning

Six patients presented after near-drowning associated cardiac arrest, of which five were severely hypothermic ($<30^{\circ}\text{C}$) at arrival to the emergency department. Half received TH although all six patients died before hospital discharge. In the late 1970s and early 1980s, the use of TH in drowned patients was advocated as part of the 'H.Y.P.E.R' therapy approach to hypoxic brain injury (hyperhydration by diuretics, hyperventilation, hypothermia to treat hyperpyrexia, barbiturates to treat hyperexcitability, and neuromuscular blockade to treat hyper-rigidity) (Bohn et al, 1986; Conn et al, 1980; Conn et al, 1978). However, the work by Bohn and colleagues highlighted the poor outcomes associated with the use of TH in submersion victims this ending the use of TH as a critical care therapy at that time (Bohn et al, 1986; Modell, 1986). Additional concerns were the use of lower levels of hypothermia therapy (30 to 32°C), poor stability of target temperature, variable duration (1 to 10 days) harmful effects of excess barbiturates and the associated increased risk of adverse side effects (e.g. arrhythmias and infection). The positive findings of subsequent animal, neonatal

and adult studies using TH at a higher (and apparently safer) temperature level (32 to 34°C), has supported TH recommendations in adult patients presenting after hypothermic cardiac arrest (Bierens et al, 2002). However, the current ongoing TH trials are excluding patients presenting with an admission temperature <32°C from entry (NCT00754481; NCT00878644; NCT00880087), therefore the answer to whether to use TH in this specific patient group, desperately in need of improved outcomes, will continue to be unclear.

7.6.3 Cardiac arrest resuscitation factors

All patients (5/73; 8%) presenting in ventricular fibrillation received TH, consistent with the stronger worded ILCOR recommendations for adolescents presenting in a shockable rhythm (Kleinman et al, 2010).

Bystander CPR was more common in the group receiving TH. The association of bystander CPR and improved survival after OHCA is not clearly defined in the literature. In chapter 6, bystander CPR was not found to be associated with increased survival. This is similar to the Australian OHCA study by Deasy et al (2010) and pooled analysis findings in the systematic review by Donoghue et al (2005), although a recent study from Japan's National Utstein Registry of the Fire and Disaster Management Agency did identify bystander CPR as predictor of good outcome at one month after OHCA in patients under one year of age (Abe et al, 2012). Difficulties in quantifying bystander CPR with regards quality, effectiveness and prior training, especially in a retrospective study, add to the complexities of interpreting the effect on outcome. However, without CPR patients after OHCA rarely survive. Therefore, evidence of attempted bystander CPR may still have given additional benefit to the TH group.

7.6.4 Seizures

Seizures were identified in only 11% (8/73) of patients with no difference between those treated with TH or ST. Formal electroencephalography (EEG) monitoring was performed in 26% (19/73) of patients with a significant increased use in TH patients. This contrasts with a prospective study of continuous EEG monitoring after cardiac arrest which reported that 47% (9/19) children receiving TH had EEG detected seizures (Abend et al, 2009). Fink et al

(2010) reported overall 17.7% seizure rate in the first four days with no difference between TH and ST groups. The differences noted between the retrospective and prospective studies may be due to difficulties in detecting and recording seizures in this population. Seizures in our study were detected through formal EEG monitoring only when there was a high suspicion by the clinical team, rather than as a routine. The use of neuromuscular blocking drugs, causing neuro-paralysis, limits the ability to clinically observe seizure muscle activity. Potentially, the use of continuous EEG monitoring during this period, as performed by Abend et al (2009), may therefore be identifying 'masked' seizure activity after hypoxic ischaemic insult. Supporting evidence from the neonatal population exists regarding a greater frequency of seizures after HIE in neonates, especially during the rewarming phase of TH application (Battin et al, 2004). Untreated seizures, particularly status epilepticus, have been associated with worsening neurological outcome in critical care patients (Friedman et al, 2009; Hosain et al, 2005). Therefore, there needs to be a high degree of vigilance with regard to identifying and treating seizures.

In our study, access to specialist EEG monitoring during the study period was restricted to office hours (9am to 4pm: Monday to Friday). This situation was similar in the study by Fink et al (2009) (personal correspondence E.Fink). However, in our institution, from 2009, a continuous EEG monitoring service was introduced which utilised amplitude integrated EEG at the bed side. This service may increase the opportunity to detect seizures, although our current data is limited and further formal evaluation is required.

7.6.5 Temperature

Core temperatures in the TH or ST group were similar in the emergency department up to first recorded temperature at PICU admission. At this time point, patients in the ST group had significantly higher temperatures (36.1°C (ST) vs. 34.3°C (TH); $p=0.007$). Due to inherent limitations of the study, it was difficult to ascertain the exact reason for this difference. Firstly, the exact start time of TH initiation was often not documented. It is possible that in the emergency department, or during transport to the PICU, the clinical team were already working towards a 'therapeutic target of hypothermia' if they anticipated, or were instructed by the admitting PICU that TH was to be performed on arrival. However, a

second possibility is the potential development of 'spontaneous hypothermia' after cardiac arrest in the TH group, as a consequence of more severe neurological injury. Spontaneous hypothermia after OHCA has been described in both adult and paediatric populations. In a study of 105 adults, who all received TH after VF cardiac arrest, temperature on admission to ICU was found to be a significant factor associated with survival (den Hartog et al, 2010). In that study, admission temperature below 35°C (the median admission temperature for the total cohort) was significantly associated with unfavourable neurological outcome (OR 3.8 (95% CI [1.3 to 11.0])). Lyon et al (2010) also reported, in a similar observational study of adult VF cardiac arrest patients treated with TH, that admission to ICU temperature was significantly higher in patients who subsequently survived to hospital discharge compared to those who died (35.7°C vs. 34.3°C; $p < 0.05$). However, in our study, in patients who received TH, lower hospital survival rates for patients admitted to PIC with a lower temperature did not reach statistical difference (22% (4/18) if $< 34.3^{\circ}\text{C}$ vs. 42% (8/19) if $\geq 34.3^{\circ}\text{C}$ ($p = 0.29$)).

The temperature measurements of the ST group showed a trend in the opposite direction. Starting with a median 'maximum' recorded level in the emergency department of 35.2 (IQR [34.2 to 36.0])°C, the ST group temperature on admission to PIC increased to just below normothermic levels (36.1 (IQR [34.0 to 37.0]) °C). We did not know what decisions were made in the emergency department regarding temperature control. However, the ability to increase the temperature in patients during this time may reflect that the patients had an intact physiological temperature control response, reflecting less severe neurological injury and therefore the converse response seen to spontaneous hypothermia as described above.

In summary, observed temperature of the TH group was lower than ST on PIC admission. The reason for the difference could be multi-factorial; however, the impact on hospital survival could not be ascertained with the current study sample size and design.

7.6.6 Therapeutic hypothermia application – induction and maintenance

Evidence from animal studies and clinical consensus is that time to target temperature after ROSC should be as short as possible, whilst avoiding unintentional overshoot to temperature $< 32^{\circ}\text{C}$. In the current study, patients receiving TH reached the target

temperature after ROSC in a median of 5.5 (IQR [3.3 to 8.5]) hours. Actual time to reach target temperature from the start of TH initiation was much quicker. Patients with admission temperature to PIC >35°C reached target temperature within a median time of 2.5 (IQR [1.75 to 4.75]) hours equating to a speed of cooling of 0.91 (IQR [0.5 to 1.5]) °C/hr.

Comparison of cooling rate with other studies is difficult. Pragmatic studies of actual clinical practice, such as this current study, often include patients who are already close to the target temperature therefore requiring minimal temperature adjustment. Therefore, we chose to express our cooling rate for patients with a start temperature >35°C. Fink et al (2010) reported a mean time to cool of only 0 hours (range 0 to 4hours); however, 60% of patients in the TH group presented at or below the target temperature. Retrospective studies also rely on temperatures recorded on charts which are often at hourly intervals. Therefore, this can decrease the precision of identifying time differences due to rounding up or down. This may account for the faster cooling time reported by Topjian et al (2010). They prospectively investigated a TH treatment protocol used in 12 patients and reported a time to reach target temperature using surface cooling of a median time of only 1.5 (IQR [1 to 1.5]) hours, although median time from arrest was similar to our current study (6 (IQR [5 to 6.5]) hours).

Another problem is that the time durations reported are not standardised. Time points recorded are often arrest time or ROSC time and time reaching target temperature only and do not necessarily record when cooling methods are applied or how they are adjusted or supplemented (e.g. addition of ice packs or use of a second cooling blanket). This process, unless prospectively collected, is often not recorded in medical records or nursing charts. For example, adult literature reports wide variability in cooling rates. The HACA study reported time to target temperature in the TH group of 8 (IQR [4 to 16]) hours at a rate of 0.3°C/hour, compared to the Australian RCT where target temperature was reached in 2.5 (IQR [1.1 to 4]) hours; at a rate of 1.5°C/hour. Both studies used surface cooling, although this was started by paramedics in the field after ROSC during the Australian study and in the ED in the HACA study. The wide difference in cooling rates between these two studies is due to the delay in starting the therapy and a direct comparison of the actual cooling rates when the therapy is applied cannot be ascertained. This problem is increased in

retrospective studies where the decision making processes are also not recorded, so we are not able to know what human factors may play a part in the speed of cooling.

Unintentional overshoot in temperature to $<32^{\circ}\text{C}$ occurred in 11% (4/38) of patients. This compares favourably to the proportion unintentionally overcooled by Fink et al (2010) (15%; 6/40), Doherty et al (2009) (17%; 5/29) and was significantly less than Topjian et al (2010) (75%; 9/12). Increased mortality has been reported in subgroups who are overcooled (Fink et al, 2010) although the causal association has not been established. Our use of servo-controlled cooling units, rather than manual temperature control by applying surface ice-packs, may account for the reduction in unintentional overshoot.

Finally, rapid reduction in temperature may additionally reflect more severe neurological injury. Patients with the fastest time to target temperature in the study by Haugh et al (2011) were reported to have a worse survival outcome compared to those where cooling time was slower.

Hypothermia was maintained for 22.5 (IQR [16.5 to 24.7]) hours using servo-controlled Blanketroll II units, consistent with ILCOR recommendations. Assessment of stability of maintenance therapy was not possible owing to frequency of data time points (four hourly). Therefore, for formal assessment of temperature stability control with surface cooling methods in the wide range of paediatric patient weights and sizes, prospective continuous temperature monitoring will be required.

In summary, our study reported similar length of time to reach target temperature and rate of temperature reduction after commencing cooling compared to other paediatric and adult studies. In addition, the method of cooling used in this study resulted in a low proportion of patients unintentionally being overcooled. Although full interpretation of factors influencing temperature reduction, TH initiation, actual cooling rates of surface cooling devices for different sized paediatric patients and temperature variability were not available, a prospective study will be required to evaluate this further.

7.6.7 Therapeutic hypothermia application – rewarming

Controlled rewarming and the avoidance of overshoot hyperthermia ($>38^{\circ}\text{C}$) are required to prevent haemodynamic instability, rapid electrolyte changes and worsening of neurological injury. Too rapid rewarming in experimental animal models has been demonstrated to increase neurological injury and reverse any advantages gained by applying TH (Hildebrand et al, 2005; Alam et al, 2006; Maxwell et al, 2005; Matsushita et al, 2001) and in humans, an additional harmful effect of rebound hyperthermia includes the loss of cerebrovascular auto-regulation (Lavinio et al, 2007). Finally, electrolyte imbalance (e.g. hyperkalaemia) can also occur through rapid intracellular shift without sufficient time for renal elimination (Polderman et al, 2001). In this study, patients were rewarmed at a rate of 0.3 (IQR [0.23 to 0.44]) $^{\circ}\text{C}/\text{hour}$, and only 32% re-warmed less than or equal to 0.25 $^{\circ}\text{C}/\text{hour}$. The optimal rewarming rate after TH in humans has not been established. There has been a decrease in the rewarming rates used in clinical studies of TH after cardiac arrest, TBI and stroke over the past 10 years. In TBI and stroke patients, where intracranial pressure monitoring has been possible, detrimental rises in intracranial pressure and reduction in cerebral perfusion pressure have been noted during rewarming, which have been associated with worse neurological outcome and incidence of cerebral herniation (Steiner et al, 2001). The reported rewarming rates in post cardiac arrest trials vary from 1 $^{\circ}\text{C}/\text{hour}$ to 0.25 $^{\circ}\text{C}/\text{hour}$; however, much slower rates have been used in TBI and stroke (e.g. 1 $^{\circ}\text{C}$ every 24 hours). Standardised rewarming rates may also be inappropriate. Some researchers advocate using surrogate measurements of cerebral perfusion and blood flow with trans-cranial doppler ultrasound to guide rewarming rate after cardiac arrest, allowing a more bespoke approach and responding to individual patients' improvements in cerebral blood flow (Ringe et al, 2011)

Hyperthermia ($>38^{\circ}\text{C}$) in the first 24 hours after rewarming occurred in 29% (10/34) patients. Evidence to support strong recommendations for avoiding hyperthermia after acute brain injury and potential detrimental effects was outlined in Chapter 6. Therefore, this finding is of concern. The incidence of hyperthermia may reflect continued rewarming effects after normothermia was reached or too rapid rewarming rates, in addition to the tendency of

hyperthermia to occur after brain injury (Bembea et al, 2010; Hickey et al, 2000; Busch et al, 2006). However, it is not clear whether patients in our study continued to be actively temperature controlled with servo-controlled cooling devices after rewarming. Rebound hyperthermia has also been reported with other methods of rewarming such as 74% of adults using the endovascular cooling catheters (Pichon et al, 2007). Our study demonstrates a controlled rewarming rate close to the current recommend rates for post cardiac arrest TH management; however, rebound hyperthermia was still common. Strict monitoring of both temperature control and physiological effects of rewarming are essential during TH. No human study has investigated the optimum rate of rewarming after TH for neurological injury and further evaluation of this important part of the therapy is required.

7.6.8 Physiological differences

Reduction in core temperature in humans is known to be associated with a concomitant reduction in heart rate in sedated patients (Polderman & Herold, 2009; Thoresen & Whitelaw, 2000). Myocardial contractility in euvoaemic patients can improve although diastolic function may be slightly impaired. The reduction in metabolic demand is normally greater than the reduced cardiac output so supply and demand remain constant or improve (Polderman & Herold, 2009). This phenomenon can be used clinically in the treatment of tachyarrhythmias after cardiac surgery (Kelly et al, 2010) and at an extreme level is an essential response to ensure survival in hibernating animals (Ahmad et al, 1979). Bradycardia and hypotension is therefore a consistent finding in studies of TH, irrespective of underlying disease process (Bernard et al, 2002; HACA, 2002; Jacobs et al, 2007; Hutchison et al, 2008; Azzopardi et al, 2009). The bradycardia is often asymptomatic and does not require treatment. However, the management of the associated hypotension is more controversial, with current TH studies and TH protocols advocating blood pressure maintenance at age appropriate levels, especially during re-warming.

In the current study, overall heart rate was significantly lower in the TH versus the ST group during the first 24 hours of PICU admission. However, the difference was not significant when the values were normalised for age, despite the overall ages of the TH and ST groups being similar. This lack of statistical difference may be due to inclusion of heart rate values

during the induction and rewarming phases of TH as well as the small sample size. We did observe an increase in proportion with bradycardia (<10th centile) in the TH group, consistent with the findings of other TH studies, with no reported associated problems.

Mean and systolic blood pressures were similar for both TH and ST groups, when compared between the first 24 hours and subsequent 48 hour time period. However, more patients in the TH group received inotropic support (74% versus 54%; $p=0.08$) which may have contributed to the maintenance of normal blood pressure range in line with the clinical objectives and also may have caused an increase in heart rate relative to age.

TH (32-34°C) can lead to thrombocytopaenia, although affects on the clotting cascade are not usually seen until lower temperatures (<30°C) are reached (Polderman & Herold, 2009). No previous TH study using a 32-34°C target has reported an increase in bleeding, although it should be noted that all studies excluded patients with active bleeding at trial enrolment and study size may have been insufficiently large to identify this risk. Median platelet count fell in both TH and ST patients across the two time periods with a slight increase in the proportion with thrombocytopaenia. However, this study did not identify an association between TH and worsening thrombocytopaenia. There was also no deterioration in prothrombin time and activated partial thromboplastin time, as expected at this level of hypothermia.

No clinically significant differences in electrolyte levels were identified between TH and ST patients, although magnesium levels were noted to drop below normal level in the second time period for both TH and ST patients. Electrolyte loss can occur secondary to increased renal excretion as a consequence of tubular insufficiency and intracellular electrolyte shift during TH (Polderman et al, 2001). We identified a reduction in plasma magnesium levels in both TH and ST patients over time, although not in sodium or potassium. Development of hypomagnesaemia has been associated with increased mortality in critically ill patients and mitigating further neurological injury (Soliman et al, 2003; Polderman et al, 2003). Maintaining normal magnesium levels may also reduce TH induced shivering. Therefore, although we did not identify an increased loss of magnesium in patients undergoing TH

compared to ST, this is a potential area requiring improvement in post cardiac arrest management.

Plasma glucose levels were initially raised and then reduced over the two time periods, although no difference between TH and ST patients was identified. Despite this, Insulin use was twice as common in the TH group. Hypothermia can cause insulin resistance and hyperglycaemia with increased requirement of insulin in patients receiving TH after cardiac arrest (Fink et al, 2010; Bernard et al, 2002). However, an additional explanation for increased insulin may have been due to a concurrent randomised controlled trial of tight versus liberal glucose control, being performed on the PICU from May 2008 onwards. This influenced insulin strategy for patients in and out of the trial during that time (ISRCTN61735247).

Hypocarbica occurred in nearly 50% of both TH and ST patients in the first 24 hours of the study using alpha stat (non-temperature adjusted) measurement. If corrected for temperature the TH PaCO₂ values would be lower (Murkin, 2007). Our hypocarbica rates were similar to an observational adult study of TH post OHCA which reported that severe hypocarbica (PaCO₂ <4kPa) occurred in 46% (56/122) of samples during TH (Falkenbach et al, 2009). However, they were unable to draw conclusions regarding the association of hypocarbica and outcome due to other confounding factors.

This observation of such a high proportion with severe hypocarbica is of concern as cerebral blood flow is affected by variations in PaCO₂ and hypocarbica causes cerebral vasoconstriction and a reduction in cerebral perfusion. In addition, cerebral autoregulation controlling cerebral blood flow can be lost after hypoxic ischaemic brain injury which, combined with the detrimental effect of hypocarbica, can result in significant secondary neurological injury (Sundgreen et al, 2001; Murkin, 2007; Pappas et al, 2011). We did not find an effect on survival outcome but further improvement in ventilation management of post cardiac arrest patients appears important with more formal evaluation of the optimal PaCO₂ target after OHCA.

7.6.9 Withdrawal of life sustaining critical care support

TH has changed the traditional timing of clinical, electrophysiological and neuro-imaging investigation to predict outcome after hypoxic ischaemic brain injury (Abend et al, 2012; Young, 2009; Nakagawa et al, 2011; Fugate et al, 2010). Pharmacological clearance of sedative drugs is also delayed by TH and therefore alters timing for neurological and brain death testing (Webb & Samuels, 2011). As a consequence PICU length of stay is prolonged in patients who do not survive as a result of devastating neurological injury but whose respiratory and cardiovascular systems are supportable by modern invasive critical care therapies.

Length of PICU stay in our cohort was significantly longer in patients who received TH and did not survive (4.1 (IQR [2.6 to 5.2]) days) compared to ST non-survivors (1.2 (IQR [0.4 to 2.4]) days), although it was similar for survivors. The length of time to death in the ST group is significantly shorter than reported in the similar group by Doherty et al (2009) (9.0 (IQR [5.0 to 22.3]) days) and Fink et al (2010) (5 (IQR [1 to 14]) days). The potential inclusion of only OHCA patients in our study, with associated worse hypoxic-ischaemic injury, may account for this difference. It is possible that end-of-life management of patients and families between different countries also differed. There was also a temporal trend of increasing time to withdrawal of intensive care support and death along with an increased use of MRI and EEG monitoring. This may reflect a change in clinical practice when predicting outcome with an increased use (and potential reliance) of multi-modal methods of prediction occurring over time.

The health care cost of TH has been evaluated in adults with an estimated cost of US\$100,000 per quality adjusted life year, although this is in the context of the therapy being shown to be beneficial in post VF arrest adults (Merchant et al, 2009). In paediatrics the health care costs of TH are not known and the current on-going therapeutic hypothermia trials in the USA (THAPCA studies) are not undertaking formal health economic evaluation (NCT00878644; NCT00880087). However, the demonstrated increase in PICU length of stay (and associated costs) with TH use in this study indicates that health care costs will be rising with a change towards TH use but without clear clinical benefits. Therefore, to quantify

cost-effectiveness of TH properly, accurate and prospective evaluation of health care costs is needed in combination with a therapeutic intervention study of the clinical efficacy of TH.

7.6.10 Limitations

This study is affected by the same four limitations outlined in detail in chapter 6; being a retrospective study, with a small sample size, data collection limited to available data and a lack of neurological outcome data. We were also unable to fully adjust for selection bias and effects of temporal trend including the increasing numbers of patients per year over the study period.c195

7.6.11 Limitations – single centre study

We only included patients from a single centre. This may have had the advantage of reducing the variability of post cardiac arrest management that was demonstrated in Chapter 6, and enabled a comparison between TH and ST whilst minimising additional confounders. However, this approach potentially limits the general applicability of the overall findings to the wider UK population. Also, even within a single centre, we identified changes in post-cardiac arrest management over the seven year study period. Therapeutic hypothermia use, MRI neuro-imaging and neuro-electrophysiological (EEG/CFAM) monitoring all significantly increased in the second half of the study. There may also have been other changes that we were unable to identify, potentially confounding the overall findings of the study. For example, in 2005 new international resuscitation guidelines were published in an attempt to improve clinical practice (ILCOR, 2005). Our study was not designed to identify these changes and may have been too small to detect small changes in outcome rates. We are therefore unable to assess this impact, although other studies have also failed to demonstrate an impact on survival through the implementation of these guidelines (Deasy et al, 2011b; Fonte et al, 2011; Bigham et al, 2011).

7.6.12 Limitation - Temperature monitoring

When considering the implication of temperature on patients with neurological disease, knowledge of the brain temperature would of course be the ideal. Our current practice and this current study used core-temperature (oesophageal or rectal) as a surrogate for brain

temperature. Direct brain temperature monitoring is currently too invasive and therefore not possible in most paediatric neurological conditions, including hypoxic ischaemic injury after cardiac arrest. Patients after traumatic brain injury, through the use of temperature probes incorporated within intracranial pressure monitors, can have single site brain temperature monitored (Polderman, 2008; Rumana et al, 1998; Møllergaard & Nordström, 1991; Verlooy et al, 1995; Nybo et al, 2002). In this group of patients, brain temperature has been shown to exceed core temperature by as much as 2°C, possibly due to hyper-metabolism in injured areas triggered by the excitotoxic cascade and cerebral thermopooling. This phenomenon may occur in the injured brain after cardiac arrest, although this is yet to be investigated. Also the effects of surface or invasive cooling methods on human brain temperature are not known. There are additional non-invasive methods to measure brain temperature such as the zero-gradient method (Simbruner et al, 1994) and Proton Magnetic Resonance Spectroscopy temperature measurement (Cady et al, 1995; Corbett et al, 1997; Jayasundar & Singh, 2002). Therefore, these non-invasive methods may be potential investigational tools, able to assess the actual brain temperature of post-cardiac arrest patients and be feasible during the administration of whole body cooling TH.

7.7 CONCLUSION

This is the largest study to date comparing the effects of TH with ST after OHCA. TH was effectively administered in the paediatric population with limited adverse effects. Half of patients reached target temperature by 5.5 hours with a low proportion of unintentional hypothermia although post therapy hyperthermia was a common problem. We identified a temporal trend of increasing TH use with resultant increase in PICU length of stay and adjunctive neurological imaging and investigations. However, TH did not increase survival to hospital discharge in patients with similar clinical presentations to a group receiving ST.

In the paediatric population, further prospective evaluation is necessary to support the use of TH for post-OHCA patients. Current recommendations should stress the avoidance of excess hypothermia ($<32^{\circ}\text{C}$) and hyperthermia ($>38^{\circ}\text{C}$) and the goal of maintaining a 'Goldilocks Temperature' – not too hot and not too cold. However, the definitive answer to the ideal temperature remains unknown. Further studies are required to demonstrate whether TH is cost-effectiveness, safe and importantly improves the proportion of patients with good neurological survival after OHCA.

Table 7-16 Chapter 7 and RCT feasibility

What have we learnt from this study towards the feasibility of a UK randomised controlled trial?

There remains no paediatric specific evidence supporting the use of TH after OHCA in children

TH can be administered in the clinical setting within a median of 5.5 hours; however, factors affecting delay are not fully understood.

Patients experiencing extreme hypothermia ($<32^{\circ}\text{C}$) before or after PIC admission did not survive. Causal association with mortality is not defined; however, avoidance of unintentional overshoot during hypothermia induction is strongly recommended.

TH prolongs PIC length of stay compared to ST, increasing health care associated costs. Cost-effectiveness evaluation of TH is therefore essential in addition to demonstrating clinical benefit.

In 2010, 80% of OHCA patients received TH as standard care at Birmingham Children's Hospital

7.8 ACKNOWLEDGEMENT

I acknowledge the efforts of the following individuals who assisted with data collection and entry at Birmingham Children's Hospital: Ms Jessica Gosney, Ms Victoria Sanders and Dr Richard Skone. In addition to the clerical support gathering medical records of Mr Kashif Ali and Ms Hayley Osmani at Birmingham Children's Hospital.

7.9 CONTRIBUTORSHIP

Dr Scholefield (BS) designed the current study protocol, data collection tool and database. Data collection was performed by BS, Ms Jessica Gosney, Ms Victoria Sanders and Dr Richard Skone. Data cleaning, validation and queries were performed by BS. All statistical analysis and drafting of chapter content was performed by BS. Dr Paul Davies provided statistical advice. Study design and Interpretation of data was performed with supervisory assistance from Drs Morris & Duncan and Prof Gao-Smith. Final draft of chapter was additionally reviewed by Prof Gavin Perkins.

8 Summary and conclusion

“Now this is not the end. It is not even the beginning of the end.

But it is, perhaps, the end of the beginning.”

Sir Winston Churchill (British Politician: Born 1874)

8.1 OVERVIEW

Therapeutic hypothermia is a potential therapy to improve the survival rate and increase the proportion of patients with a good neurological outcome after paediatric cardiac arrest. To demonstrate its efficacy, a randomised controlled trial (RCT) recruiting infants and children would be required. Therefore, this thesis aimed to assess the feasibility of performing a RCT of therapeutic hypothermia for neuroprotection after paediatric cardiac arrest in the UK through a programme of research. The broad feasibility questions; should we, could we and how would we conduct a RCT were evaluated through eight thesis research questions. To answer these questions the following studies were undertaken; a systematic Cochrane review of the paediatric literature (Chapter 3), two surveys of clinical practice in paediatric intensive care and emergency medicine (Chapter 4), an epidemiological study of post cardiac arrest admissions to UK PICUs (Chapter 5), a multicentre, retrospective, cohort study of post cardiac arrest management (Chapter 6) and a single centre, retrospective, cohort study of therapeutic hypothermia and standard temperature management (Chapter 7). No single study provided the answer but the accumulation of the information (with acknowledged limitations) can answer the research questions summarised below.

8.2 RESEARCH QUESTIONS

8.2.1 Is there currently sufficient evidence to support (or refute) the beneficial effects of therapeutic hypothermia after paediatric cardiac arrest?

A systematic review of current literature regarding the use of hypothermia for neuroprotection in children after cardiopulmonary resuscitation was performed using Cochrane methodology. This review confirmed that there is currently no published RCT data examining therapeutic hypothermia as a neuroprotection therapy in children after cardiac arrest. Four paediatric RCTs are currently on-going or finished and awaiting analysis. Two of these are large multicentre trials (NCT00878644; NCT00880087) examining the benefits of therapeutic hypothermia ($33\pm1^{\circ}\text{C}$) versus normothermia ($36.75\pm0.75^{\circ}\text{C}$) after out of hospital and in hospital cardiac arrest separately. They have been successfully funded through national funding organisations. Clinicians have successfully recruited patients to these trials,

although only in North America and Canada. Publication of findings from these trials is not expected until 2014/2015 at the earliest, although the study is aiming to demonstrate a 14% absolute improvement in survival with good neurological outcome which may be unrealistic in a heterogeneous patient population. The review concludes that there is not enough evidence to support (or refute) the beneficial effects of therapeutic hypothermia after paediatric cardiac arrest; however, absence of evidence does not mean that there is evidence of no effect. Therefore, the review supports the need for continued research within the paediatric age group.

An additional benefit of the process of conducting the Cochrane review is personal communication with international experts across the world. This revealed a willingness to advise upon, participate in, and support our endeavours towards performing a RCT of therapeutic hypothermia after paediatric cardiac arrest.

8.2.2 What is currently practiced in the UK regarding therapeutic hypothermia after paediatric cardiac arrest?

In Chapter 4, two surveys were conducted to establish the current practice of targeted temperature management and future trial acceptability amongst paediatric intensive care (n=149) and paediatric emergency care consultants (n=77). Both groups of clinicians have key roles in post cardiac arrest patient management and decision making regarding therapeutic practices and enrolment of their patients into interventional studies. The surveys concluded that at the time of questioning, approximately half of UK paediatric intensive care consultants used therapeutic hypothermia after paediatric cardiac arrest. It was infrequently used in the emergency department, and if used, often only after advice from a paediatric intensivist. There was also wide variation in the temperature, duration and rewarming rate of therapeutic hypothermia used amongst responders, reflecting the lack of clear evidence and recommended protocols in paediatrics.

Chapter 6 also demonstrated the variation in the use of therapeutic hypothermia. The retrospective, cohort study of infants (older than 24 hours) and children (before their 16th birthday) admitted to three large UK PICUs after OHCA over a seven year period (January

2004 to December 2010), showed wide variation in the proportion of infants and children receiving therapeutic hypothermia. In Unit 1 only 6% (3/50) of OHCA patients received TH compared with Unit 3 (22%, 7/32) and Unit 2 (52%, 38/73). This confirmed that the self-reported variation in behaviour found in the survey was supported by variation in actual clinical behaviour.

8.2.3 Does clinical equipoise exist amongst the paediatric intensive and emergency care communities?

This fundamental question was also explored in Chapter 4 and forms the foundation as to whether clinicians will support a RCT and be willing to recruit patients. When specifically asked regarding clinical equipoise, 73% of paediatric intensivists and 52% of emergency medicine physicians agreed or strongly agreed to have clinical equipoise regarding the ideal post resuscitation temperature management and would randomly assign patients to therapeutic hypothermia or normothermia therapy. The lower agreement from the emergency physicians was accompanied by a larger proportion claiming a neutral view as opposed to disagreement. In addition to clinical equipoise, there was strong support for a RCT and for consultants to enrol their own patients into this. The variation in actual clinical use of therapeutic hypothermia, demonstrated between three units in Chapter 6, also supports the position of clinical equipoise. However, in Chapter 7, the use of therapeutic hypothermia was shown to increase significantly over the study period at Birmingham Children's Hospital and by 2010, 80% of OHCA patients received the therapy. Therefore, the position of clinical equipoise may be changing and this will require constant review.

The paediatric intensivist and emergency medicine surveys were conducted in November 2008 and June 2010, respectively. Very little new paediatric literature has emerged since conducting these surveys to influence clinicians' views. Nevertheless, it will be necessary to re-investigate clinical equipoise during a consultation process regarding protocol design and individual PICU participation in a potential trial. In addition, agreement to participate in a

RCT was made without knowledge of the trial protocol. A formal agreement to participate would be required after full explanation of the trial design.

8.2.4 What is the current epidemiology of children who are successfully resuscitated and admitted to PICU after cardiac arrest in the UK?

Through the extraction and analysis of IHCA and OHCA PICU admissions from the prospectively collected national PICANet database study in Chapter 5, information on 1703 children was obtained from 30 PICUs in the UK and Eire between January 2003 and June 2010.

The incidence rate of OHCA admissions to PICU was 1.3 per 100,000 children (0 to 15 years) per year; however, it was not possible to calculate an IHCA incidence rate. IHCA and OHCA each accounted for 0.8% (IQR [0.6–1.0]) of all PICU admissions. PICU survival was significantly higher for IHCA patients (76% versus 50%; $p < 0.01$) and higher than other comparable published studies.

Differences between IHCA and OHCA were reported, justifying the need for separation of the two populations in a RCT. IHCA patients were younger, had more pre-existing chronic conditions and less patients had two unresponsive pupils. For both IHCA and OHCA patients, two unresponsive pupils, the use of vasoactive drugs, presence of certain chronic conditions or transfer from another hospital to PICU all affected survival.

For non-survivors in particular, treatment with therapeutic hypothermia may increase both length of ventilation and PICU stay especially when allowing time for formal neurological assessment. This may have a significant effect on both families and potential health care related costs which should be evaluated in future studies.

Additional data regarding OHCA patients were reported from Chapter 6. The three PICUs admitted approximately 21% of all infants and children requiring PICU in the UK. This study reported lower survival rates after OHCA compared with the PICANet data (32% (50/155) versus 50% (423/841) and significantly higher rates of patients with two unresponsive pupils (84% versus 22%). This increases the concerns regarding the limitations of the PICANet database and the potential errors in classification and categorisation of post cardiac arrest

patients from the database. The significance of these differences is in relation to the actual number of post cardiac arrest admissions and the baseline rate of survival after OHCA. Both these factors are fundamental to the sample size and effect size estimations, potentially causing an underestimation, although not to a magnitude likely to affect the overall conclusion of the following question.

8.2.5 What is the potential size of the paediatric post-cardiac arrest population admitted to PICU and is this sufficient for a UK RCT of therapeutic hypothermia?

Cardiac arrest rates and estimation of required study sample size for an intervention study indicates that the UK would not be able to perform the trial without international collaboration. To demonstrate a possible 10% absolute treatment effect in a UK interventional trial after IHCA and OHCA would take at least 3.7 and 6.9 years respectively involving 66% (20/30) of the largest UK PICUs. However, even with an optimistic ratio of 50% identified patients being entered into a study, the UK would require funding for nearly 14 years to recruit to an OHCA study and 7.5 years for an IHCA study using 20 PICUs to demonstrate a realistic 10% difference in outcome. After adjusting for the lower survival rate after OHCA observed in Chapter 6 and 7, the UK population would still be insufficient to recruit to a UK only RCT.

An option for the UK would be to perform an RCT with an objective to 'supplement' the patient numbers in the current THAPCA in-hospital and out of hospital cardiac arrest studies. These two studies are aiming to show a 14% absolute effect size change in the primary outcome. By performing a UK study, the additional patient numbers achievable within three to four years, if combined with the THAPCA study, could demonstrate an absolute effect size change closer to 11%. For example, using the baseline hospital survival rate in the ST group of 23% (Chapter 7), an estimated 11% treatment effect size and absolute increase in hospital survival with TH (absolute difference seen in Chapter 7), 80% power ($1-\beta$) and within a 95% confidence level (α level), a future study would require 264 patients in each arm (i.e. 528 patients in total). Compared to the target of 350 patients recruited to the THAPCA out of hospital cardiac arrest study (NCT00878644), this is an additional 178

patients. This number of patients is an achievable target in the UK and although the smaller UK study would not be large enough to demonstrate a clear difference on its own, information in a different health care system would be gained, increasing the general applicability of the RCT findings.

Experience from the neonatal HIE trials is that individual RCTs have failed to demonstrate statistically significant benefit from TH. Only through meta-analysis of a number of RCTs has the impressive improvement in survival and neurological outcome been demonstrated (Edwards et al, 2010). In another example, three European RCTs of decompressive craniectomy for middle cerebral artery infarction were examined in a pooled, individual patient data meta-analysis, prior to completion of the studies (Vahedi et al, 2007). This was owing to slow enrolment and conflicting interim analyses of the individual studies regarding the benefits and harm of surgery. Therefore, the meta-analysis aimed to avoid unnecessary (and unethical) continuation of randomisation in the individual trials and allowed a conclusive result to be reported much sooner.

The major barrier to this approach would be gaining national funding for a RCT which would be anticipated to not be sufficiently large to demonstrate a treatment effect on its own. A realistic response from funders could therefore be to wait for the publication of the THAPCA studies prior to starting a UK study. Whether this would be the correct approach is extremely difficult to predict. The delay may increase the time taken to gain a definitive answer to whether therapeutic hypothermia is beneficial, thereby subjecting more patients to a potentially harmful therapy. However, waiting for the THACPA study results may also be the correct one if the trial produces a definitive answer.

8.2.6 Can outcome after paediatric cardiac arrest be predicted to assist risk-stratification of patients in a RCT?

Prediction of outcome after cardiac arrest will be of value in determining potential inclusion and exclusion criteria for an intervention trial, and a prediction tool could be used in a risk-stratified analysis of the RCT population.

In Chapter 6, identified variables, associated with PIC survival, were analysed and included in a multivariate logistic regression model and Correlation and Regression Tree (CART) analysis to create a prediction tool. One hundred and fifty five OHCA patients met study entry criteria. 32% (50/155) survived to PIC discharge. A multivariate logistic regression model with factors available before and during resuscitation identified presenting in a shockable rhythm as strongly associated with survival. Including factors available up to four hours after PIC admission, raised blood lactate level and two unresponsive pupils were identified as strong predictors of mortality. The CART analysis prediction tool also added the duration of cardiac arrest as an additional discriminator to blood lactate level and two unresponsive pupils to create a more practical prediction tool for bedside use.

The next step would be prospective validation of the prediction tools in a larger OHCA population. This could be performed within a RCT or in a large prospective observational study. The use of the tool in a risk-stratified analysis may improve the ability (and statistical power) to detect sub groups in a study who are likely to benefit or be harmed by the treatment, rather than assuming an average effect across the total trial population. Chapter 6 has demonstrated the heterogeneous nature of paediatric OHCA patients, with a wide variation in aetiologies, co-morbid conditions and resuscitation related factors affecting survival. Therefore, paediatric cardiac arrest research appears to be an ideal area in which to evaluate improved methods for risk-stratifying and adjusting for the potentially confounding variables in this complex patient population.

8.2.7 Can therapeutic hypothermia be implemented quickly, safely and consistently in children?

Important features of therapeutic hypothermia delivery have been identified in animal and clinical studies; rapid commencement and induction of cooling, avoidance of extreme overshoot hypothermia ($<32^{\circ}\text{C}$), stable maintenance period and controlled gradual rewarming to normothermia avoiding rebound hyperthermia ($>38^{\circ}\text{C}$). Therefore, assessment of how quickly patients are admitted to a PICU, how quickly therapeutic hypothermia is commenced and target temperature reached, and assessment of adverse events directly or

indirectly related to the therapeutic hypothermia is important to maximise the potential benefit of the therapy.

In Chapter 6, median time to admission at the three PICUs after OHCA was four and a half hours, and involved 73% being transferred from a large number of different referring hospitals. This will greatly reduce the time remaining within the therapeutic window, currently postulated to be six hours post cardiac arrest, in order to approach, recruit and randomise patients into a RCT after arrival to PICU.

In Chapter 4, emergency department physicians expressed a willingness to be part of a RCT of post cardiac arrest TH and most emergency departments had suitable equipment to maintain or reduce temperatures. However, the infrequency of resuscitated paediatric cardiac arrest patients in the majority of hospitals admitting children would make this logistically very difficult. Early recruitment will ideally require input by specialist transport teams who attend the secondary hospital and transfer the patients to the tertiary PICU. The increasing retrieval service infrastructure in the UK, with dedicated transport networks, should increase the feasibility of recruiting patients and implement a research protocol.

Chapter 7 compared the use of therapeutic hypothermia with standard temperature therapy after paediatric OHCA. This was a retrospective cohort study set in a UK tertiary PICU including infants and children greater than 24 hours until their 16th birthday admitted to PICU after an OHCA (January 2004 to December 2010). In patients receiving TH (n=38), return of spontaneous circulation to target temperature duration was 5.5 (IQR[1.5-8]) hours, demonstrating that current single centre practice enabled at least 50% of patients to be at the maintenance phase of TH within the six hour 'therapeutic window'. If core temperature at the start of TH induction was greater than 35°C, target temperature was reached within 2.5 (IQR[2-4]) hours at a rate of 0.9 (IQR[0.5-1.5]) °C/hr, an induction rate consistent with other paediatric studies (Topjian et al, 2011). Median TH target temperature was 33.5°C (33-34°C) for a duration of 22:30 (IQR [16:37 to 24:44]) hours:minutes. Rewarming lasted 10:30 (IQR [07:00 to 14:45]) hours:minutes at a rate of 0.3 (IQR [0.23-0.45]) °C/hr.

Eleven percent of patients experienced overshoot hypothermia ($<32^{\circ}\text{C}$) during induction and 29% hyperthermia ($>38^{\circ}\text{C}$) after rewarming. Patients experiencing extreme hypothermia ($<32^{\circ}\text{C}$) before or after PIC admission did not survive, although a causal association could not be established. The demonstration of instability in temperature control reinforces the need for further evaluation of induction and rewarming techniques in addition to strict treatment protocols. The potential relationship with extreme hypothermia and hyperthermia and worse outcome necessitates improved control during these key stages of therapy in a prospective study, in order to eliminate the confounding effect on outcome.

8.2.8 Does therapeutic hypothermia improve survival after out of hospital cardiac arrest and are there significant physiological adverse effects?

In Chapter 7, there was no demonstrated difference in hospital survival between patients treated with TH versus ST (34% vs. 23%; $p=0.284$). Compared to ST, the TH group only differed with respect to receiving more bystander CPR, a trend towards longer duration of cardiac arrest and a lower core temperature at PIC admission. There remains no paediatric specific evidence supporting the use of TH after OHCA in children. This study reconfirms the findings of the two previously published retrospective cohort studies that TH did not improve survival outcome after OHCA cardiac arrest, even when comparing two populations more closely matched (Doherty et al, 2009; Fink et al, 2010).

We did not identify significant physiological differences or adverse events between patients treated with TH and ST. A significant reduction in plasma magnesium and high rates of hypocarbia were observed in both groups and warrant further evaluation due to the theoretical improvement in outcome which may be observed if these are better controlled. Also, the study did not show any increase in adverse events in patients receiving TH. However, the retrospective design of the study may have limited its ability to identify all adverse events and this will require further prospective evaluation.

8.3 FUTURE DIRECTIONS FOR RESEARCH

“No research will answer all queries that the future may raise. It is wiser to praise the work for what it has accomplished and then to formulate the problems still to be solved.”

Theobald Smith (American epidemiologist; Born 1859)

The question of whether therapeutic hypothermia after paediatric cardiac arrest is the correct treatment remains an important and unanswered question for children and the UK National Health Service. The next step following this thesis will be to consider whether to develop a protocol for a RCT of therapeutic hypothermia versus normothermia after paediatric cardiac arrest using the wealth of knowledge gained through the research studies presented here. The major barrier of patient numbers could be overcome by international collaboration. Previous successful partnerships with Canadian, Australian, New Zealand and European paediatric critical care research networks may facilitate this process. However, the problems in securing funding for a multi-million pound study and the legislative barriers that will be faced will make this a very difficult option. The second option of a ‘supplementary’ UK study to support the US THAPCA study has already been discussed, including the funding concerns which will be faced in performing a UK study too small to demonstrate a significant difference in the primary outcome. Waiting to run the next paediatric therapeutic hypothermia trial until the publication of the THAPCA studies in three to four years time may be the preferred option by the funders, especially with current limited health research finances.

In addition to a definitive RCT, this thesis has identified a number of other key areas requiring further research of both paediatric cardiac arrest and our understanding of therapeutic hypothermia. Chapter 5 identified the strengths and limitation of the PICANet database. Development of this database to include data collection of key Utstein defined resuscitation variables, post-cardiac arrest interventions occurring on PICU (e.g. therapeutic hypothermia) and neurological outcome status of patients admitted to PICU would be a significant advancement. PICANet is supported by all UK PICUs and already has validation and data monitoring processes in place. This simple increase in data collection, even for a

limited period of time, would provide an extremely useful source and allow better interpretation of cardiac arrest management and the relationship with both survival and neurological outcome.

The prediction tool developed in Chapter 6 also requires validation in a larger prospective population. A simple and achievable method to collect this data would be through the enhanced PICANet database described above. Even with only a limited increase in cardiac arrest and resuscitation variables (length of cardiac arrest, admission lactate, presenting rhythm and use of therapeutic hypothermia) a rapid validation of the tool could be performed. This would be the ideal situation, prior to using it for as a risk-stratified randomisation or minimisation tool within a RCT.

Feasibility of TH application, induction, maintenance and rewarming was demonstrated in Chapter 7. However, it was not possible to define the factors which can improve the speed of TH commencement and the optimum method of inducing and maintaining TH. A prospective evaluation of TH application with collection of data examining human factors, environmental factors, equipment factors and patients related factors on the impact of TH administration would be ideal. In addition, a comparative study of re-warming rates and control of overshoot hyperthermia would also significantly add to an understudied area of therapeutic hypothermia research.

Chapter 7 also identified that seizure rates after OHCA appeared lower than other studies (Abend et al, 2009; Fink et al, 2010); however, patients were not monitored continuously during periods of neuromuscular blockade and electroconvulsive seizures may have been missed. Neonatal and paediatric intensive care use of amplitude integrated EEG (aEEG, a bedside, simplified, continuous EEG monitor) is evolving and may be ideal for post cardiac arrest patients. A prospective evaluation of post cardiac arrest patients would enable an assessment of whether potentially detrimental seizures are being missed and whether seizure recognition and early treatment can improve neurological outcome.

Increased requirement and length of paediatric intensive care, with associated cost has been identified with the increased use of TH but without demonstrating a significant increase in survival. TH also delays the window for current neurological prognostication. In this study

a high proportion of patients received active withdrawal of intensive care support after clinicians and families accepted that continued treatment was futile. Therefore, in addition to the clinical criteria proposed in the prediction tool, continued investigation of early prognostic biomarkers such as: plasma biomarkers (S100B, neurone specific endolase), radiological imaging (MRI and Magnetic Resonance Spectroscopy) and neurophysiological monitoring (aEEG/EEG) may improve our understanding of who may benefit from prolonged treatment with TH. It is also recommended when conducting these studies, that the process of withdrawal of intensive support, decision making and documentation becomes standardised (Nielsen et al, 2011).

8.4 CONCLUSION

Is it feasible to perform a post cardiac arrest, randomised controlled trial of therapeutic hypothermia for neuroprotection in UK children? Posing the questions: should we, could we and if so, how would we?

First, should we perform a post cardiac arrest, randomised controlled trial of therapeutic hypothermia for neuroprotection in UK children? The answer is yes. This thesis has demonstrated through a systematic review of the literature and questioning the medical community on current knowledge and position of clinical equipoise, that there is insufficient paediatric specific evidence to inform current clinical practice but a desire and support to conduct further research. A retrospective comparison of therapeutic hypothermia and standard temperature therapy in two similar post OHCA paediatric populations is presented but did not show a significant increase in survival with therapeutic hypothermia. Cardiac arrest in children remains a devastating condition and further research to improve survival rates and neurological outcomes are still desperately needed.

Secondly, could we perform a post cardiac arrest, randomised controlled trial of therapeutic hypothermia for neuroprotection in UK children? The answer is not on our own. The UK post cardiac arrest paediatric population is too small to recruit to a RCT large enough to be able to demonstrate a realistic treatment effect size change without a long and expensive study. Especially as IHCA and OHCA patients would be studied separately and appropriate inclusion and exclusion criteria are required to minimise heterogeneity. However, a smaller RCT could be performed within the UK, supplementing the on-going THAPCA studies ((NCT00878644; NCT00880087), by using similar outcome measures and allowing future meta-analysis, ideally with individual patient data.

Finally, how would we perform a post cardiac arrest, randomised controlled trial of therapeutic hypothermia for neuroprotection in UK children? The outcome prediction tool utilising post resuscitation factors and clinical information at the time of PICU admission will allow risk-stratification of patients during recruitment and in post-trial analysis. Recruitment of patients transferred from secondary hospital would require trial involvement by regional

transport teams to ensure enrolment within the theoretical narrow therapeutic window. Current use of therapeutic hypothermia reported in this thesis requires improvement to minimise potential increased harm associated with extreme hypothermia ($<32^{\circ}\text{C}$) and rebound hyperthermia ($>38^{\circ}\text{C}$). However, induction rates, duration of treatment, temperature and rewarming rates were satisfactory in patients receiving therapeutic hypothermia and the current method could be used in a future study.

Further research is needed, including the development of a RCT protocol in addition to assessing the chances of UK national funding of a study prior to the publication of the THAPCA studies. Enhancement of the current PICANet database may be one simple method to improve our understanding of paediatric cardiac arrest and post cardiac arrest management in the UK. It is hoped that the research conducted for this thesis will be the beginning of further progress to improve the outcome of children suffering cardiac arrest.

9 Appendix

“Not only is an ‘appendix’ useless, but it is sometimes the cause of death”

In. The Descent of Man and Selection in Relation to Sex.

Charles Darwin (English naturalist, born 1809)

9.1 Systematic review search terms

9.1.1 Ovid MEDLINE search strategy

1. exp Hypothermia/ or exp Hypothermia, Induced/ or hypothermia.mp. or (cooling or temperature regulat*).ti,ab.
2. exp Heart Arrest/ or Ventricular Fibrillation/ or Cardiopulmonary Resuscitation/ or Tachycardia, Ventricular/ or neuroprotection.mp. or asystole.ti,ab. or dysrhythmia.mp. or ((heart or cardiac or ventricular or circulatory) adj3 arrest).mp. or (ventricular adj5 (fibrillation or tachycardia or arrhythmia)).mp. or pulseless electrical activity.mp. or electromechanical dissociation.mp. or cardiopulmonary resuscitation.mp. or (PEA or EMD or OOHCA).ti,ab. or non-perfusing rhythm.mp.
3. 1 and 2
4. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (animals not (humans and animals)).sh.
5. 3 and 4

9.1.2 Search strategy for CENTRAL, the Cochrane Library

- #1 MeSH descriptor Hypothermia explode all trees
- #2 MeSH descriptor Hypothermia, Induced explode all trees
- #3 hypothermia or (cooling or (temperature near (low or regulat*))) or hibernat* or cryotherapy or refrigeration).ti,ab
- #4 (#1 OR #2 OR #3)
- #5 MeSH descriptor Heart Arrest explode all trees
- #6 MeSH descriptor Ventricular Fibrillation explode all trees
- #7 MeSH descriptor Cardiopulmonary Resuscitation explode all trees
- #8 MeSH descriptor Tachycardia, Ventricular explode all trees
- #9 neuroprotection or asystole.ti,ab or distirhythmia or ((hearth or cardiac or ventricular or circulat*) near arrest) or (ventricular near (fibrillation or tachycardia or arrhythmia)) or pulseless electrical activity or electromechanical dissociation or cardiopulmonary resuscitation or (PEA or EMD or OOHCA).ti,ab or non-perfusing rhythm
- #10 (#5 OR #6 OR #7 OR #8 OR #9)
- #11 (#4 AND #10)

9.1.3 Search strategy for EMBASE (Ovid SP)

1. exp hypothermia/ or exp induced hypothermia/ or exp cryotherapy/ or hypothermia.mp. or (cooling or (temperature adj3 (low or regulat*))) or hibernat* or cryotherapy or refrigeration).ti,ab.
2. heart arrest/ or heart ventricle fibrillation/ or resuscitation/ or heart ventricle tachycardia/ or neuroprotection.mp. or asystole.ti,ab. or distirhythmia.mp. or ((hearth or cardiac or ventricular or circulat*) adj3 arrest).mp. or (ventricular adj5 (fibrillation or tachycardia or arrhythmia)).mp. or pulseless electrical activity.mp. or electromechanical dissociation.mp. or cardiopulmonary resuscitation.mp. or (PEA or EMD or OOHCA).ti,ab. or non-perfusing rhythm.mp.
3. 1 and 2
4. (placebo.sh. or controlled study.ab. or random*.ti,ab. or trial*.ti,ab. or ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*)).ti,ab.) not (animals not (humans and animals)).sh.
5. 3 and 4

9.1.4 Search strategy for CINAHL (EBSCO host)

S1 ((MH "Hypothermia") OR (MH "Hypothermia, Induced") OR (MH "Hypothermia (NANDA)") OR (MH "Cryotherapy")) OR (hypothermia or (cooling or (temperature and (low or regulat*))) or hibernat* or cryotherapy or refrigeration))

S2 ((MH "Heart Arrest") OR (MH "Ventricular Fibrillation") OR (MH "Tachycardia, Ventricular") OR (MH "Resuscitation, Cardiopulmonary")) OR (neuroprotection or asystole or distrhythmia or ((hearth or cardiac or ventricular or circulat*) and arrest) or (ventricular and (fibrillation or tachycardia or arrhythmia)) or pulseless electrical activity or electromechanical dissociation or cardiopulmonary resuscitation or (PEA or EMD or OOHCA) or non-perfusing rhythm)

S3 S1 and S2

S4 ((MH "Randomized Controlled Trials") OR (MH "Random Assignment") OR (MH "Prospective Studies") OR (MH "Multicenter Studies") OR (MH "Single-Blind Studies") OR (MH "Triple-Blind Studies") OR (MH "Double-Blind Studies") OR (MH "Clinical Trials")) OR (random* or controlled clinical trial or placebo)

S5 S3 and S4

9.1.5 Search strategy for ISI Web of Science and BIOSIS Citation Index

#1 TS=(hypothermia or (cooling or (temperature SAME (low or regulat*)) or hibernat* or cryotherapy or refrigeration))

#2 TS=(neuroprotection or asystole or distrhythmia or ((hearth or cardiac or ventricular or circulat*) and arrest) or (ventricular SAME (fibrillation or tachycardia or arrhythmia)) or pulseless electrical activity or electromechanical dissociation or cardiopulmonary resuscitation or (PEA or EMD or OOHCA) or non-perfusing rhythm)

#3 #2 AND #1

#4 TS=(random* or (controlled SAME trial*) or prospective or multicenter) or TS=((blind* or mask*) SAME (single or double or triple))

#5 #4 AND #3

9.2 Systematic review data extraction form

Study ID
Authors
Medline Journal ID
Year of Publication
Language

Type of study: RCT Cohort Case-control
(Circle relevant study type)

Comment on study design:

QUALITY OF CONCEALMENT OF RANDOM ALLOCATION

Domain	Description	Review Author's Judgement
Sequence Generation		YES / NO / UNCLEAR
Allocation concealment		YES / NO / UNCLEAR
Blinding of participants, personnel and outcome assessors. <i>Outcome:</i>		YES / NO / UNCLEAR
Blinding of participants, personnel and outcome assessors. <i>Outcome:</i>		YES / NO / UNCLEAR
Incomplete outcome data <i>Outcome:</i>		YES / NO / UNCLEAR
Incomplete outcome data <i>Outcome:</i>		YES / NO / UNCLEAR
Other sources of bias		YES / NO / UNCLEAR

INCLUSION/EXCLUSION CRITERIA

	Yes	No
Clearly defined		
Inclusion criteria		
Exclusion criteria		

PARTICIPANTS

Number of eligible participants		Number enrolled in study	
Number of males		Number of females	
Number of children <18		Number in treatment group	

	Treatment Group	Control Group
Witnessed arrest		
Time to ROSC		

INTERVENTION

	Control Group	Treatment Group
Method of cooling		
Time to Randomisation		
Time to start of cooling		
Time to target temperature		
Depth of cooling		
Length of cooling		
COMMENTS ON TREATMENT		

	Yes	No	Unclear
Withdrawals			

OUTCOME**Control Group****Treatment Group**

Days in hospital		
Ventilator Free days		
Survival to admission		
Survival to intensive care discharge		
Survival to hospital discharge		
6 months survival		
12 months survival		
Long term survival > 12 months		
Neurological outcome at Hospital discharge		
Neurological outcome at 6 months		
Neurological outcome at 12 months		
Long Term Neuro outcome > 12months		
Adverse Events		
Cost Effectiveness Evaluation		

CHANGES IN PROTOCOL**CONTACT WITH AUTHOR****COMMENTS ON THIS STUDY**

9.3 List of experts contacted for systematic review

Contact	Name	Institution
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2	Ericka Fink	University of Pittsburgh, USA
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4	Mike Dean	University of Utah, USA
5	Vinay Nadkarni	Children's Hospital of Pennsylvania, USA
6	Stephen Bernard	Alfred Hospital, Melbourne Australia
7	Fritz Sterz	University of Vienna, Austria
8	Michael Holzer	University of Vienna, Austria
9	Alexis Topjian	Children's Hospital of Pennsylvania, USA
10	Robert Tasker	Harvard University, USA
11	Hannelore Ringe	Berlin, Germany
12	Patrick Kochanek	University of Pittsburgh, USA
13	John Beca	Auckland, New Zealand
14	Marianne Thoresen	University of Bristol, UK
15	Ken Nagao	Tokyo, Japan
17	Qian Quan	Beijing, China

9.4 Published protocol for Cochrane review

Hypothermia for neuroprotection in children after cardiopulmonary arrest (Protocol)

Scholefield B, Morris K, Duncan H, Davies P, Gao Smith F, Khan K



This is a reprint of a Cochrane protocol, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2011, Issue 11

<http://www.thecochranelibrary.com>



Hypothermia for neuroprotection in children after cardiopulmonary arrest (Protocol)
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[Intervention Protocol]

Hypothermia for neuroprotection in children after cardiopulmonary arrest

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Editorial group: Cochrane Anaesthesia Group.

Publication status and date: New, published in Issue 11, 2011.

Citation: Scholefield B, Morris K, Duncan H, Davies P, Gao Smith F, Khan K. Hypothermia for neuroprotection in children after cardiopulmonary arrest. *Cochrane Database of Systematic Reviews* 2011, Issue 11. Art. No.: CD009442. DOI: 10.1002/14651858.CD009442.

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To systematically review the literature and, if feasible, perform a meta-analysis concerning the neuroprotective effects of therapeutic hypothermia after cardiac arrest in children.

To determine whether therapeutic hypothermia is effective in improving the primary outcome of good neurological survival after cardiac arrest in children and the secondary outcome of improving overall survival.

To determine the extent of adverse effects and effects on quality of life in this context.

BACKGROUND

Therapeutic hypothermia has been shown clinically to be neuroprotective in neonates with hypoxic ischaemic encephalopathy secondary to birth asphyxia (Jacobs 2007) and in adults (greater than 18 years old) after ventricular fibrillation cardiac arrest (Arrich 2009; Holzer 2005). Its role after cardiac arrest in children has not been established although the International Liaison Committee for Resuscitation guidelines recommend consideration of its use in this setting (Kleinman 2010). This systematic review of the literature will investigate the neuroprotective effects of therapeutic hypothermia in children after cardiac arrest.

Description of the condition

Cardiac arrest in children can be a devastating event. The incidence of out-of-hospital cardiac arrest (OOHCA) has been estimated to be 8 to 20/100,000 children/year with in-hospital cardiopulmonary arrest (IHCA) 100 times more frequent (Donoghue 2005; Nadkarni 2006); 2% to 6% of children admitted to a paediatric intensive care unit (PICU) have a cardiac arrest (Nadkarni 2006). Survival rates to discharge from hospital for children who suffer an IHCA are 15% to 30% whilst those who suffer an OOHCA have a worse survival rate (5% to 12%) (Donoghue 2005; Nadkarni 2006). Only 0.3% to 4% of children who suffer an OOHCA survive neurologically intact (Donoghue 2005).

Neurological consequences of hypoxic ischaemic damage to the brain range from mild concentration, attention and short-term memory problems to much more severe damage to the cerebral cortex, hippocampus, basal ganglia and cerebellum. Severe damage can result in significant long-term loss of function with development of cerebral palsy, blindness, seizures, hypothalamic and pituitary insufficiency. Very severe damage can produce a persistent vegetative state or be fatal. Those children who do survive often have significant neurological disability with resultant emotional, time and financial impacts on themselves, their families, their educational and care needs, rehabilitation and society as a whole (Duncan 2009; Morris 1993; Ronco 1995).

Neurological outcomes are often assessed by the use of the Paediatric Cerebral Performance Category (PCPC) score (Fiser 1992) (Appendix 1). The PCPC scores can classically be combined into a good outcome (PCPC 1 and 2) and poor outcome (PCPC 3 to 5). If children with preceding disability are included then a good outcome may be recorded as no change from baseline. Other neurological outcome scores, for example the Vineland Adaptive Behaviour Scales (Sparrow 1984), have also been validated for use in assessing the neurological outcomes in children.

The aetiology for paediatric cardiac arrest is different to that of adults, with respiratory disorders leading to hypoxia often preceding cardiac arrest in children (Young 2004). The neonates studied while receiving therapeutic hypothermia after hypoxic ischaemic encephalopathy often did not have a cardiac arrest and therefore

retained some cerebral blood flow in comparison to the absent cerebral blood flow during cardiac arrest (Azzopardi 2009).

Description of the intervention

Therapeutic hypothermia is defined as the process of lowering core body temperature to between 32 and 35 degrees Celsius. Therapeutic hypothermia can be administered through systemic cooling (by surface or invasive methods) and selective surface head cooling. Sedation and often neuromuscular blockade are required to tolerate the intervention and avoid shivering.

How the intervention might work

Hypothermia therapy for brain protection, applied before cerebral ischaemia, has allowed cardiac surgery to be performed under circulatory arrest states (Bigelow 1950). Clinical and experimental studies have demonstrated neuroprotective properties of therapeutic hypothermia when commenced during and after hypoxic ischaemic insults (Azzopardi 2009; Bernard 2002; Busto 1987; Colbourne 1994; Colbourne 1995; Colbourne 1999; Fink 2004; Gluckman 2005; Gunn 1997; Hypothermia After Cardiac Arrest Study Group 2002; Shankaran 2005; Shankaran 2008). However, the pathophysiological mechanism by which therapeutic hypothermia may exert its neuroprotective effect is complex. There is evidence that it modulates a number of the key biochemical, metabolic and pathophysiological events in the brain which occur after cerebral ischaemia and reperfusion. These include reduction of cerebral metabolism and balancing out energy failure by the protection of adenosine triphosphate stores (ATP) during cessation of cerebral blood flow (Steen 1983; Takasu 1996); attenuation of the biosynthesis, release and uptake of excitotoxic compounds such as glutamate and dopamine (Busto 1989; Suehiro 1999); and attenuation of the production of proteins important in apoptosis (Bax and Bcl-2) (Xu 2002; Yenari 2002). It has also been shown to reduce free radical production (Gil 1996), improve delayed hypoperfusion (Karibe 1994) and is involved in neuronal anti-inflammatory effects (Sutcliffe 2001).

Why it is important to do this review

Cardiac arrest in children is an important condition with a poor survival rate and a high chance of neurological injury leading to significant long-term impact on individuals, families and society. There are currently no interventions available to decrease neurological injury other than supportive care in the intensive care unit, which is why this evaluation is important. Paediatric specific data is needed regarding the effect of therapeutic hypothermia due to the different aetiology and resultant pathophysiology compared to adults and neonates. Therapeutic hypothermia is used by some in paediatric critical care after cardiac arrest (Haque 2006; Scholefield

2010) and a meta-analysis of the clinical trial data is therefore highly important.

OBJECTIVES

To systematically review the literature and, if feasible, perform a meta-analysis concerning the neuroprotective effects of therapeutic hypothermia after cardiac arrest in children.

To determine whether therapeutic hypothermia is effective in improving the primary outcome of good neurological survival after cardiac arrest in children and the secondary outcome of improving overall survival.

To determine the extent of adverse effects and effects on quality of life in this context.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials (RCTs) and quasi-randomized controlled trials evaluating therapeutic hypothermia as a neuroprotective intervention after cardiac arrest in children. We will exclude non-randomized studies from the meta-analysis but will provide a narrative summary of these studies in the review's discussion section (and appendices).

Types of participants

We will include all studies with children who are successfully resuscitated after a cardiac arrest in any setting. We will include neonates older than 24 hours of age and with a corrected gestational age of greater than or equal to 35 weeks, children and adolescents up to their 18th birthday. We will exclude neonates whose cardiac arrest occurs at the time of birth and adults greater than 18 years of age as these have been studied separately (Arrich 2009; Jacobs 2007) and the presumed cause of the cardiac arrest is different to children.

Types of interventions

Therapeutic hypothermia, regardless of how body temperature is reduced, applied within a few hours after return of spontaneous circulation after cardiac arrest. Therapeutic hypothermia is defined as a target temperature of 32 to 35 degrees celsius. We define the control intervention as treatment according to the standard treatment after cardiac arrest at the time of the trial.

Types of outcome measures

Primary outcomes

1. Best neurological outcome at hospital discharge and within the first year as assessed by the Paediatric Cerebral Performance Category score and other validated outcome scores for use in children (e.g. Vineland Adaptive Behaviour Scales)
2. Survival up to six months and long-term survival (long term defined as greater than one year)

Secondary outcomes

1. Survival to intensive care discharge
2. Survival to hospital discharge
3. Adverse event rates as reported by authors
4. Quality of life indicators at six months and at long term

Search methods for identification of studies

Electronic searches

We will search the Cochrane Anaesthesia Review Group Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, latest issue); Ovid MEDLINE (1966 to date); Ovid EMBASE (1980 to date); Ovid CINAHL (1982 to date); Ovid BIOSIS (1923 to date); Web of Science (1945 to date).

The Ovid MEDLINE specific search terms are described in Appendix 2. We will base the search strategies for the other databases on the one for MEDLINE. We will combine the Ovid MEDLINE and EMBASE searches with the sensitive strategies described in Section 6.4 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011) to search for RCTs. BIOSIS and Web of Science contain book articles and abstracts of conference presentations published in a wide range of relevant specialist journals.

We will not use language or publication type restrictions.

Searching other resources

We will search the bibliographies of all retrieved and relevant publications identified by these strategies for further studies. We will search the Current Controlled trials (<http://www.controlled-trials.com/>), Clinical Trials (<http://clinicaltrials.gov/>) and Trials Central (<http://www.trialscentral.org/>) databases of ongoing trials. We will search Zetoc (<http://zetoc.mimas.ac.uk/>) and OpenSIGLE (<http://opensigle.inist.fr/>), and contact experts in the field to search for any other published or unpublished literature and on-going research.

Data collection and analysis

Selection of studies

Potentially eligible studies will be located based on screening of title and abstract by two authors (BS and KM or HD). We will obtain full copies of potentially eligible studies. There will be no blinding to the journal, the authors or the institution. Two authors (BS and KM or HD), acting independently, will decide on inclusion or exclusion of studies based on predefined inclusion and exclusion forms. We will resolve disagreements by discussion. If this does not result in consensus, the third author will arbitrate.

Data extraction and management

We will extract data from eligible studies and summarize them in a data extraction sheet (Appendix 3). We will include baseline data on demographics of study and control group participants. This will include age and gender. In addition, we will extract the following information regarding the actual cardiac arrest; location, aetiology, duration of arrest; and time to return of spontaneous circulation for each group. We will record data on the intervention; time to implement intervention; duration, and type of temperature control method. The temperature of the study group and control group at the start of a study, during intervention and after the intervention will be recorded. We will also record the health-care setting in which the interventions were performed. In addition, duration of follow up and numbers lost to follow up will be extracted as well as outcomes.

All data regarding the interventions studied will be independently extracted by two authors (BS and KM or HD). We will resolve disagreements by discussion. If this does not result in consensus, the third author will arbitrate. We will contact primary authors to obtain missing data or to gain clarification.

Assessment of risk of bias in included studies

After we include all available eligible studies in the review, we will assign two authors (BS and KM or HD) to independently assess each study using The Cochrane Collaboration's tool for assessing risk of bias (Higgins 2011). We will assess six domains: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other bias (Appendix 3). We will fill out a risk of bias table for each eligible study. Any disagreement will be discussed amongst authors and consensus agreed. We will present our assessment of risk of bias using a 'risk of bias summary figure', which presents all of the judgments in a cross-tabulation of study by entry.

Measures of treatment effect

For dichotomous outcomes, we will express the estimate of effect of an intervention as the risk ratio (RR) together with the 95%

confidence interval (CI). For continuous outcomes, we will use mean differences (MD) and standard deviations and summarize the data for each group using mean differences and 95% CIs.

Unit of analysis issues

We do not anticipate unit of analysis issues.

Dealing with missing data

If data are missing from trial reports BS will attempt to contact the original investigator for additional data. Where there are missing data, we will 'impute' and carry out a sensitivity analysis between studies in which data were 'imputed' for an intention-to-treat (ITT) analysis assuming that all missing participants experienced the event, or that all missing participants did not experience the event.

Assessment of heterogeneity

We will judge clinical heterogeneity, in particular in the application of therapeutic hypothermia, and the results will be noted in the review. If significant clinical heterogeneity exists, pooling of data will not be done; the data from individual studies will be presented in a tabular format. We will test for statistical heterogeneity using visible inspection of the forest plot and the I^2 statistic (Higgins 2011). We will consider an I^2 statistic > 50% as significant statistical heterogeneity and a value < 25% will be considered ignorable statistical heterogeneity.

Assessment of reporting biases

We will assess risk of reporting bias by producing a funnel plot if there are sufficient number of included studies (more than 10). We will take the following steps to reduce reporting bias.

1. Searching of multiple databases, trial registries and conference proceedings as described above.
2. Applying no language restriction.
3. Excluding duplicate reports of the same study to avoid duplication bias.

Data synthesis

We will summarize the aims, methods and outcome measures of interest (neurological outcome, mortality, adverse events and quality of life indicators) for each included study. We will express the outcome measures of interest for survivors relative to non-survivors as the risk ratio (RR).

For both dichotomous and continuous data we will undertake a meta-analysis using a random-effects method with inverse variance. We will perform a sensitivity analysis by comparing this with a meta-analysis using a fixed-effect method with inverse variance. We plan to use data at the aggregate (study) level.

Subgroup analysis and investigation of heterogeneity

We will perform subgroup analysis on the following variables if the data can be extracted from included studies.

1. Age and sex.
2. Method of inducing therapeutic hypothermia (systemic cooling versus selective head cooling).
3. Location of arrest (in-hospital versus out-of-hospital arrest).
4. Duration of intervention.
5. Delay to induction of therapeutic hypothermia (less than six hours versus greater than six hours).
6. Rate of rewarming after therapeutic hypothermia.
7. First presenting cardiac rhythm (ventricular fibrillation OR pulseless ventricular tachycardia versus asystole OR pulseless electrical activity).

Meta-regression will not be performed due to the anticipation of a small number of included trials.

Sensitivity analysis

We plan to undertake sensitivity analysis between studies in which data were 'imputed' for ITT analysis, assuming that all missing participants experienced the event or that all missing participants did not experience the event.

Summary of findings table

We will use the principles of the GRADE system (Guyatt 2008) to assess the quality of the body of evidence associated with specific outcomes:

1. best neurological outcome,
2. survival to intensive care discharge,
3. survival to hospital discharge,
4. survival up to six months,
5. long-term survival.

in our review we will construct a 'Summary of findings' (SoF) table using the GRADE software. The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence takes into consideration within study risk of bias (methodologic quality), the directness of the evidence, heterogeneity of the data, precision of effect estimates and risk of publication bias.

ACKNOWLEDGEMENTS

We would like to thank Jane Cracknell and Karen Hovhannisyan from the Cochrane Anaesthetic Review Group for their help and editorial advice during the preparation of this protocol. We would also like to thank Mathew Zacharias (content editor), Nathan Pace (statistical editor), Jasmin Arrich, Alexis Topjian and Ronan O'Sullivan (peer reviewers).

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* Indicates the major publication for the study

APPENDICES

Appendix 1. Paediatric Cerebral Performance Category

The Paediatric Cerebral Performance Categories (PCPC) are as follows (Fiser 1992).

PCPC 1: Normal cerebral performance. Normal at age appropriate level, school age child attends regular school classroom.

PCPC 2: Mild Disability. Conscious alert and able to interact at an age appropriate level, school age child attending school classroom but grade perhaps not appropriate for age. May have mild neurological deficit.

PCPC 3: Moderate disability. Conscious, sufficient cerebral function for age appropriate independent activities of daily life. School age child attending special education classroom. May have learning disability.

PCPC 4: Severe disability. Conscious, dependent on others for daily support because of impaired brain function.

PCPC 5: Coma or vegetative state. Any degree of coma without any of the criteria for brain death. Unawareness even if awake in appearance without interaction with the environment. Cerebral unresponsiveness. No evidence of cortical activity and not aroused by verbal stimuli. Possibly some reflexive responses spontaneous eye opening and/or sleep-wake cycles.

PCPC 6: Brain death.

9.5 Survey one questionnaire

Questionnaire regarding the use of induced hypothermia as a therapy after cardiac arrest in children for paediatric intensive care consultants

Please answer the following questions using the options available

1) Do you believe that the use of therapeutic hypothermia after cardiac arrest in children results in improved survival? Yes/No/Don't know

2) Do you use induced hypothermia as a therapy after resuscitation from cardiac arrest in children who have a return of spontaneous circulation? Never/Seldom/Often/Always

a) If you answered Never or Seldom: Which of the following describe your reason for not using therapeutic hypothermia after resuscitation from cardiac arrest? [you may choose more than one]

- Do not look after post-cardiac arrest patients
- Not enough research evidence
- Not part of APLS guidelines
- Too technically difficult
- Patient consent concerns
- Cooling method too slow
- Not considered it as a therapy
- Initial attempts unsatisfactory

If you answered Never to question 2 please proceed to question 17, otherwise please proceed to question 3.

3) Does your clinical practice change if the child has an in-hospital cardiac arrest rather than an out-of hospital cardiac arrest? Yes/No

4) Do you induce hypothermia as a therapy after in-hospital cardiac arrest in children? Never/Seldom/Often/Always

5) Do you induce hypothermia as a therapy after out-of-hospital cardiac arrest in children? Never/Seldom/Often/Always

6) Does your unit have a specific protocol for implementing hypothermia therapy? Yes/No/Don't know

7) Which method of cooling do you commonly use to induce hypothermia? [you may choose more than one]

- Air blanket
- Ice-cold [4°C] intravenous fluid
- Ice packs to skin
- Wet linen
- Water blanket
- Intravascular cooling device

8) Which method of cooling do you use to maintain hypothermia? [you may choose more than one]

- Air blanket
- Ice-cold [4°C] intravenous fluid
- Ice packs to skin

- Wet linen
- Water blanket
- Intravascular cooling device

9) Where would you actively start to induce hypothermia in your patients?

- The Emergency Department Yes/No
- Referring hospital prior to transfer Yes/No
- The Intensive care unit. Yes/No

10) Do you have a fixed length of time [as opposed to variable length] you would routinely maintain hypothermia? Yes/No

11) How long do you routinely maintain hypothermia? [please specify hours if fixed and range of hours if variable]hours

12) What temperature do you aim to cool to?

- 36-37 °C
- 35-36 °C
- 34-35 °C
- 33-34 °C
- 32-33 °C
- <32 °C

13) Do you control the speed of rewarming? Yes/No

14) If yes what is your target rate for rewarming?..... °C/hr

15) Do you use active rewarming devices? Yes/No

16) Which [if any] of the following influences your current use of hypothermia as a therapy after cardiac arrest? [you can select more than one]

a. Length of time to return of spontaneous circulation (ROSC) after effective CPR.
Yes/No/Don't know

If yes please select the group of patients you would consider starting hypothermia therapy

- ROSC after < 5 mins
- ROSC after 5 - 10mins
- ROSC after 10 – 20 mins
- ROSC after 20 – 30 mins
- ROSC after 30 – 60 mins
- ROSC after > 60 mins

b. Whether the arrest was witnessed or not Yes/No/Don't know

If yes please select the group of patients you would consider starting hypothermia therapy

- Witnessed cardiac arrest
- Unwitnessed cardiac arrest

c. Age of patient Yes/No/Don't know

If yes please select the group of patients you would consider starting hypothermia therapy

- Less than 7 days old
- 7 to 28 days
- 28 days to 1 year
- 1 to 5 years
- 5 to 10 year
- Older than 10 years

d. Pupillary reaction [in patient who had not received Atropine] Yes/No/Don't know

If yes please select the group of patients you would consider starting hypothermia therapy

- Fixed and dilated pupils immediately after return of spontaneous circulation (ROSC)
- Fixed and dilated pupils 1 hour after ROSC
- Reactive pupils immediately after ROSC

e. Delay between ROSC and opportunity to start hypothermia therapy Yes/No/Don't know

If yes please select the group of patients you would consider starting hypothermia therapy

- Delay of 1 hour post ROSC before being able to commence hypothermia
- Delay of 4 hours
- Delay of 6 hours
- Delay of 12 hours
- Delay of 24 hours

Please enter where appropriate your agreement of the following statements using the scale of: Strongly agree/Agree/No opinion or neutral/Disagree/Strongly disagree.

17) The publication of a large randomised controlled trial currently being designed in the USA in the use of hypothermia in children after cardiac arrest would convince me of the benefit or lack of benefit for its use in my patient population?

Strongly agree/Agree/No opinion or neutral/Disagree/Strongly disagree

18) A multi-centre randomised controlled trial conducted in the United Kingdom in the use of hypothermia in children after cardiac arrest is necessary in addition to a USA study to convince me of its use in my patient population?

Strongly agree/Agree/No opinion or neutral/Disagree/Strongly disagree

19) I currently feel there is clinical equipoise regarding the use of hypothermia versus normothermia after cardiac arrest in children.

[Clinical equipoise: defined as 'there existing an honest, professional disagreement among expert clinicians about the preferred treatment'] Freedman B. Equipoise and the ethics of clinical research. NEnglJMed. 1987 Jul 16;317(3):141-5.

Strongly agree/Agree/No opinion or neutral/Disagree/Strongly disagree

20) Would you support a randomised controlled trial in the UK investigating the use of hypothermia after cardiac arrest in children comparing -

- a) Hypothermia therapy versus normothermia? Yes/No/Don't know
- b) Variation in duration of hypothermia e.g. 24 versus 48 hours? Yes/No/Don't know
- c) Variation in method of inducing and maintaining hypothermia e.g. use of cold [4°C] intravenous saline versus cooling blankets? Yes/No/Don't know

21) It is ethical to perform a randomised controlled trial of hypothermia therapy in children after cardiac arrest?

Strongly agree/Agree/No opinion or neutral/Disagree/Strongly disagree

22) It is ethical to use deferred consent in clinical trials investigating therapies immediately after cardiac arrest?

Deferred consent: defined as 'obtaining Informed consent [from parent or guardian] as soon as reasonably practicable after the initial emergency. This would be a requirement of continued participation in the trial; but its absence would not preclude initial entry into a trial. The use of deferred consent would only be used after specific approval by an ethics committee.'

Strongly agree/Agree/No opinion or neutral/Disagree/Strongly disagree

23) In a randomised controlled trial of hypothermia versus normothermia after cardiac arrest the following are important clinical outcome measures.

Answer for the following: Strongly agree/Agree/No opinion or neutral/Disagree/Strongly disagree

- Mortality
- Neurological outcome
- Adverse events from induced hypothermia [e.g. sepsis, ARDS, coagulopathy]
- Length of stay in PICU
- Ventilator free days

24) Would you randomise your patients to a multi-centre UK study of hypothermia after cardiac arrest in children? Yes/No/Don't know

25) Do you feel the use of hypothermia as a therapy should be recorded on PICANet data collection records? Yes/No/Don't know

26) Please indicate your current clinical position:

- full time consultant in PICU
- Consultant with some sessions in PICU
- Length of time as consultant (years)

9.6 Survey two questionnaire

Survey of the use of therapeutic hypothermia after cardiac arrest in UK paediatric emergency departments.

Demographics

- 1) Which of the following best describes your current role?
 - a) Consultant in Emergency Medicine
 - b) Consultant in Paediatric Emergency Medicine
 - c) Consultant in Emergency Medicine with dual accreditation in Paediatrics
- 2) Which of the following best describes your Emergency Department?
 - a) Paediatric Emergency Department within a Tertiary Children's Hospital
 - b) Emergency Department with Audio-Visual separation of children and adults
 - c) Emergency Department with no Audio-Visual separation of children and adults
 Other (please specify)
- 3) On average how many children are seen in your Emergency Department per year?
- 4) Are children who have suffered a cardiac arrest managed in your Emergency Department?
 - a) Yes
 - b) No

Current practice in Therapeutic Hypothermia

- 5) Are you aware of the published research regarding the use of therapeutic hypothermia in adults (18 yrs) who have a return of spontaneous circulation (ROSC) following out-of-hospital cardiac arrest?
 - a) Yes
 - b) No
- 6) Do you use therapeutic hypothermia as a therapy for adults (>18 yrs) who have a return of spontaneous circulation (ROSC) following out-of-hospital cardiac arrest?
 - a) Never
 - b) Seldom
 - c) Often
 - d) Always
 - e) N/A
- 7) Does your Emergency Department have a specific protocol for implementing hypothermia therapy in adults >18 yrs?
 - a) Yes
 - b) No
 - c) Don't know
- 8) Does your Emergency Department have a specific protocol for implementing hypothermia therapy in children <16 yrs?
 - a) Yes
 - b) No

c) Don't know

9) Do you currently have access to any of the equipment listed below in your Emergency Department which could be used to induce therapeutic hypothermia in a child? (you can select more than one)

- a) Cold air circulating blanket
- b) Ice Cold (4°Celsius) intravenous fluid
- c) Ice packs to be applied to skin
- d) Wet linen
- e) Cold water circulating Blanket
- f) Intravascular cooling device

Other (please specify)

10) Do you believe that the use of therapeutic hypothermia after cardiac arrest in children (<16 yrs) improves clinical outcome?

- a) Yes
- b) No
- c) Don't know

11) In the management of children (<16yrs) who have had or shown a return of spontaneous circulation (ROSC) following resuscitation from cardiac arrest, how often do you use therapeutic hypothermia in your Emergency Department?

- a) Never
- b) Seldom
- c) Often
- d) Always

If you answered 'Often' or 'Always' proceed directly to question 13.

12) Which of the following describes your reason(s) for not using therapeutic hypothermia after resuscitation from paediatric cardiac arrest? (you can select more than one)

- a) I do not look after patients post cardiac arrest
- b) There is not enough research evidence to support its use
- c) Therapeutic hypothermia is not in the APLS guidelines
- d) Therapeutic hypothermia is technically too difficult to initiate
- e) I have concerns that patients are unable to give informed consent
- f) The cooling method to which I have access is too slow
- g) I have never considered hypothermia as a therapy in post arrest children
- h) Hypothermia is not advocated by my local Paediatric Intensive Care Unit
- i) I do not have any equipment available to initiate cooling

Other (please specify)

13) Which method(s) of cooling do you commonly use to induce hypothermia (all age groups)? (you can select more than one)

- a) Cold air circulating blanket
- b) Ice Cold (4°Celsius) intravenous fluid
- c) Ice packs applied to skin
- d) Wet linen
- e) Cold water circulating Blanket
- f) Intravascular cooling device

Other (please specify)

14) What temperature (degrees celcius) do you aim to cool to?

- a) 36-36.9
- b) 35-35.9
- c) 34-34.9
- d) 33-33.9
- e) 32-32.9
- f) 31-31.9
- g) 30-30.9
- h) Don't know

15) On what basis do you select patients to induce therapeutic hypothermia? (you can select more than one)

- a) Likelihood of patient recovery after the arrest
- b) Absence of life limiting condition
- c) Absence of need for vasoactive drug support
- d) Presence of coma for >1hr post successful resuscitation
- e) Availability of equipment
- f) On advice from PICU
- g) Don't know

Other (please specify)

Research Opinion/Support

Regarding the following statements, please select whether you: Strongly agree, Agree, No opinion or Neutral, Disagree, Strongly disagree

16) There is clinical equipoise regarding the use of therapeutic hypothermia versus normothermia after cardiac arrest in children?

(Clinical Equipoise: defined as "the existence of an honest, professional disagreement among expert clinicians about the preferred treatment") Freedman B: Equipoise and the ethics of clinical research. N Engl J Med 1987 Jul 16;317(3): 414-5

- a) Strongly agree
- b) Agree
- c) No opinion or Neutral
- d) Disagree
- e) Strongly disagree

17) It is ethical to perform a randomized controlled trial of hypothermia in children after cardiac arrest

- a) Strongly agree
- b) Agree
- c) No opinion or Neutral
- d) Disagree
- e) Strongly disagree

18) It is ethical to use deferred consent in clinical trials investigating therapies commenced immediately after cardiac arrest

(Deferred consent: defined as "Obtaining informed consent (from parent or guardian) as soon as is reasonably practicable after the initial emergency. This would be a requirement of continued participation in the trial; but its absence would not preclude initial entry into a trial.

The use of deferred consent would only be used after specific approval by an ethics committee")

- a) Strongly agree
- b) Agree
- c) No opinion or Neutral
- d) Disagree
- e) Strongly disagree

19) Would you support a randomized controlled trial in the UK investigating the use of hypothermia after cardiac arrest in children comparing:

a. Hypothermia versus Normothermia

- a) Yes
- b) No
- c) Don't know

b. Variation in the method of inducing and maintaining hypothermia

- a) Yes
- b) No
- c) Don't know

20) Would you, in principle, allow your patients in the Emergency Department to be included into a multi-centre randomized UK study of hypothermia after cardiac arrest in children?

- a) Yes
- b) No
- c) Don't know

If you answered 'No' could you briefly explain your answer?

21) Would you be willing to commence therapeutic hypothermia in your Emergency Department as part of a research protocol?

- a) Yes
- b) No
- c) Don't know

If you answered 'No' or 'Don't know' could you briefly explain your answer?

Please write any further comments you have regarding the use of hypothermia after cardiac arrest in children and the prospect of future UK research and your involvement in this area:

9.7 Published paper: Survey of the use of therapeutic hypothermia post cardiac arrest

Downloaded from adc.bmj.com on June 5, 2012 - Published by group.bmj.com

Original article

Survey of the use of therapeutic hypothermia post cardiac arrest

Barnaby R Scholefield, Heather P Duncan, Kevin P Morris

► A supplementary appendix is published online only. To view this file visit the journal online (<http://adc.bmj.com>)

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Accepted 15 February 2010

ABSTRACT

Objectives Therapeutic hypothermia improves neurological outcome in adults after ventricular fibrillation cardiac arrest and neonates with hypoxic ischaemic encephalopathy. There is currently no clinical research to support its use in the paediatric population. This survey aims to ascertain current practice in the UK, and attitudes and opinions to guide the feasibility of a UK multicentre, randomised, controlled trial of therapeutic hypothermia after cardiac arrest in children (The Cold-PACK Post Arrest Cooling in Kids study).

Methods Anonymous survey of UK paediatric intensive care consultants (n=149).

Results A total of 113 (76%) of 149 surveys were returned; 65% responded that they do not know if therapeutic hypothermia improves survival after cardiac arrest. Despite this, 48% 'always' or 'often' use therapeutic hypothermia after return of spontaneous circulation following cardiac arrest in children. Among those who never use therapeutic hypothermia (33%) the commonest explanation given was 'not enough research evidence' (91%). With respect to the dose of therapeutic hypothermia the median duration of cooling used is 24–48 h (range 4–72 h) and median target temperature 34°C to 35°C (range 32°C to 37°C); 68% target a temperature range higher than that applied in the published adult and neonatal studies (33±1°C). There was strong support for a trial of therapeutic hypothermia being ethical (89%) and using deferred consent (85%).

Conclusions Wide variation in UK practice in the use of therapeutic hypothermia and a state of clinical equipoise is demonstrated by this survey, which shows important support for UK multicentre collaboration in a future trial of therapeutic hypothermia after cardiac arrest.

INTRODUCTION

Therapeutic hypothermia to 33±1°C instigated after return of spontaneous circulation (ROSC) in adults who remain comatose 1 h after ventricular fibrillation cardiac arrest has been shown to significantly improve neurological outcome.^{1–2} Four large trials have also demonstrated that 72 h of therapeutic hypothermia improves neurological outcome in newborns with hypoxic ischaemic encephalopathy.^{3–6}

The use of therapeutic hypothermia after cardiac arrest in children has not been adequately studied to date. Despite this the International Liaison Committee for Resuscitation (ILCOR) recommend considering the use of therapeutic hypothermia for 12–24 h in children who remain comatose after resuscitation from paediatric cardiac arrest; presumably extrapolating from neonatal and adult literature.⁷

An anonymous web-based survey conducted in North America highlighted wide variation of

What is already known on this topic

- Therapeutic hypothermia is an established treatment for neonates with hypoxic ischaemic encephalopathy after birth and adults after ventricular fibrillation cardiac arrest.
- There is little published research on the use of therapeutic hypothermia after paediatric cardiac arrest and wide variation in its use.

What this study adds

- In the UK approximately half of paediatric intensive care consultants currently use therapeutic hypothermia after paediatric cardiac arrest.
- There is wide variation in the duration and depth of therapeutic hypothermia used.
- Support for future UK multicentre research is currently present.

practice in paediatric intensive care units concerning when therapeutic hypothermia is started and how it is administered.⁸ As this survey was undertaken 5 years ago, with little input from UK intensivists and a poor overall response rate (12%), it does not provide an accurate picture of current UK practice. This survey aims to ascertain current practice in the UK and attitudes and opinions to guide the feasibility of a UK multicentre, randomised, controlled trial of therapeutic hypothermia after cardiac arrest in children (The Cold-PACK Post Arrest Cooling in Kids study).

METHODS

Survey development

Relevant questions were generated by the study group and piloted on a group of 10 paediatric intensive care (PIC) consultants from 3 hospitals for further feedback and hyperlink access testing.

Survey execution

In all, 149 PIC consultants from 25 UK Paediatric Intensive Care Units (PICUs) were identified. An invitation to participate was sent out on 1 October 2008. Links to the survey were sent out a further three times and the website was closed on the 23 November 2008.

Survey template

This was created using Microsoft ASP.NET 2008 (Microsoft, Seattle, Washington, USA). Microsoft Excel (Microsoft, Seattle, Washington, USA) was used for data analysis and results are presented as percentage of survey responders, or mean (SD).

RESULTS

Of 149 consultants surveyed, 113 responses (76%) were received.

Consultants responded to questions about their current use of therapeutic hypothermia (table 1), how they select patients (table 1), what 'dose' of hypothermia they use (table 1), methods of cooling (table 2) and their views on further research (table 1).

Use of therapeutic hypothermia

A total of 65% reported not knowing if therapeutic hypothermia after cardiac arrest improves survival; 48% always or often use therapeutic hypothermia with the remaining 52% stating they seldom or never use it. The commonest reason given by those who seldom or never use hypothermia was 'not enough research evidence' (91%).

Patient selection

A total of 65% of PIC consultants who have used therapeutic hypothermia would not change their practice according to whether the cardiac arrest occurred in or out of hospital.

The time to ROSC after cardiac arrest was influential in decision making for 66% (table 1). A higher proportion would commence therapeutic hypothermia for ROSC times between 5 and 30 min, though 23% would even consider therapeutic hypothermia for a ROSC delay exceeding 60 min.

Methods of inducing and maintaining therapeutic hypothermia

A total of 90% of PIC consultants do not have a protocol for the use of therapeutic hypothermia in their unit.

Various combinations of cooling methods were reported, with a circulating water blanket the most commonly used (78%) (table 2).

'Dose' of hypothermia

Duration

The stated duration of induced hypothermia ranged from 4 to 96 h. The maximum duration of cooling used is shown in figure 1.

Table 1 Responses to individual questions and statements from questionnaire (see supplementary appendix)

Category and question	Parameters			
	n	Yes, % (n)	No, % (n)	Don't know, % (n)
Use of therapeutic hypothermia				
Do you believe that therapeutic hypothermia improves survival after cardiac arrest in children?	113	26 (29)	10 (11)	65 (73)
Does your clinical practice change if the child has an in-hospital cardiac arrest rather than an out-of-hospital cardiac arrest?	78*	35 (27)	65 (51)	
		Never, % (n)	Seldom, % (n)	Often, % (n)
Do you use induced hypothermia as a therapy after resuscitation from cardiac arrest in children who have a return of spontaneous circulation?	113	33 (37)	19 (22)	39 (44)
Do you induce hypothermia as a therapy after in-hospital cardiac arrest in children?	77*	1 (1)	39 (30)	47 (36)
Do you induce hypothermia as a therapy after out-of-hospital cardiac arrest in children?	76*	5 (4)	25 (19)	46 (35)
Patient selection and dose of hypothermia				
Which (if any) of the following influences your current use of hypothermia as a therapy after cardiac arrest? (you can select more than one)		Yes, % (n)	No, % (n)	Don't know, % (n)
ROSC	76	66 (50)	28 (21)	7 (5)
Delayed opportunity to cool	74	30 (22)	57 (42)	14 (10)
Witnessing arrest	76	28 (21)	61 (46)	12 (9)
Pupillary reaction	74	27 (20)	62 (46)	11 (8)
Age	76	3 (2)	90 (68)	8 (6)
Does your unit have a specific protocol for implementing hypothermia therapy?	76	7 (5)	90 (69)	3 (2)
Where would you actively start to induce hypothermia in your patients?				
Emergency department	73	33 (24)	67 (49)	
Referring hospital	74	46 (34)	54 (40)	
Intensive care unit	77	100 (77)	0 (0)	
Do you have a fixed length of time (as opposed to variable length) you would routinely maintain hypothermia?	75	44 (33)	56 (42)	
Do you control the speed of rewarming?	76	50 (38)	50 (38)	
Do you use active rewarming devices?	77	25 (19)	75 (58)	
Opinions regarding statements on current and further research				
The publication of a large randomised controlled trial currently being designed in the USA in the use of hypothermia in children after cardiac arrest would convince me of the benefit or lack of benefit for its use in my patient population	n	Mean†	SD	Agreement, %‡
A multicentre randomised controlled trial conducted in the UK in the use of hypothermia in children after cardiac arrest is necessary in addition to a US study to convince me of its use in my patient population	113	3.2	±1.1	47
I currently feel there is clinical equipoise regarding the use of hypothermia versus normothermia after cardiac arrest in children	113	3.8	±0.8	73
It is ethical to perform a randomised controlled trial of hypothermia therapy in children after cardiac arrest	111	4.2	±0.9	89
It is ethical to use deferred consent in clinical trials investigating therapies immediately after cardiac arrest	113	4.1	±0.9	88

*Response from those who 'always', 'often' or 'seldom' use therapeutic hypothermia only.

†Mean score on a Likert scale from 5 (strongly agree) to 1 (strongly disagree) ±SD.

‡Agreement=percentage responding 'agree' or 'strongly agree'.

Original article

The majority cool for a duration of up to 24–48 h (85%) with 15% having a maximum cooling time longer than 48 h.

Depth of cooling

This ranged from 32 to 37°C with only 33% targeting 33±1°C (figure 2). The two responders (3%) who stated 36°C to 37°C commented that they use cooling methods to actively avoid hyperthermia rather than to induce hypothermia.

Speed of rewarming

This was controlled by 50% of responders with a range of 0.1°C to 1.0°C/h given as the target temperature increase.

Views on future research into therapeutic hypothermia

There continues to be a state of clinical equipoise in the UK regarding the use of therapeutic hypothermia after cardiac arrest according to 73% of PIC consultants.

A total of 86% would randomise their patients into a randomised controlled trial (RCT) of therapeutic hypothermia in cardiac arrest. There was greatest support for a comparative trial of hypothermia versus normothermia. There was strong support for a RCT of therapeutic hypothermia being ethical (89%) and using deferred consent (85%).

Although 83% of those surveyed felt that publication of a large multicentre study undertaken in the USA would inform them of the benefit or lack of benefit of therapeutic hypothermia to their own patient population, 46% agree that a UK trial is needed in addition to a US trial.

DISCUSSION

This survey suggests that there is wide variation in the use of therapeutic hypothermia after cardiac arrest in children in PICUs in the UK. Approximately 50% of PIC consultants report 'always' or 'often' using it, despite an absence of published, paediatric specific, literature to support its use. There is however an ILCOR recommendation 'to consider the use of therapeutic hypothermia after cardiac arrest in children'.⁷ The evidence in animal, neonatal and adult literature, although promising for those patient groups and specific conditions, has

limitations when transferred to the paediatric cardiac arrest population.

Simple surface methods of cooling were used by all responders, with the majority reporting using more than one method. Of interest is the small number (5%) who reported to use 4°C iced intravenous saline to induce therapeutic hypothermia, a method demonstrated to be safe and effective in adult pilot studies of therapeutic hypothermia^{9–11} and one paediatric case report.¹²

The 'dose' of hypothermia appears to be an important element in the potential efficacy of therapeutic hypothermia. The wide variation in duration and depth of cooling and also rate of rewarming reflects the lack of clear evidence. Very few centres reported following a unit protocol that would assist in unifying centre practice. Uncertainty may also be present after the reporting of a trend towards increased harm with the use of hypothermia in the Hypothermia after Paediatric Head Injury (Hyp-HIT) trial.¹³

A total of 86% of PIC consultants stated they select a duration of cooling between 24 and 48 h although durations outside this range are also considered. The two adult therapeutic hypothermia RCTs used 12 or 24 h duration^{1,2} while the neonatal studies of hypoxic ischaemic encephalopathy have used 72 h duration.^{3–6} This survey demonstrates a stated duration of treatment falling between the two sets of published data. Without specific safety data in children the potential risks of longer duration of cooling are not known.

In all, 74% of PIC consultants feel there is still clinical equipoise for the use of therapeutic hypothermia after cardiac arrest

Table 2 Methods of inducing therapeutic hypothermia

Method of cooling	Percentage*(n)
Water blanket	78 (59)
Ice packs to skin	62 (47)
Air blanket	42 (32)
Intravascular cooling device	8 (6)
Wet linen	5 (4)
Intravenous iced saline	5 (4)

*Percentage total greater than 100 as option to select multiple methods.

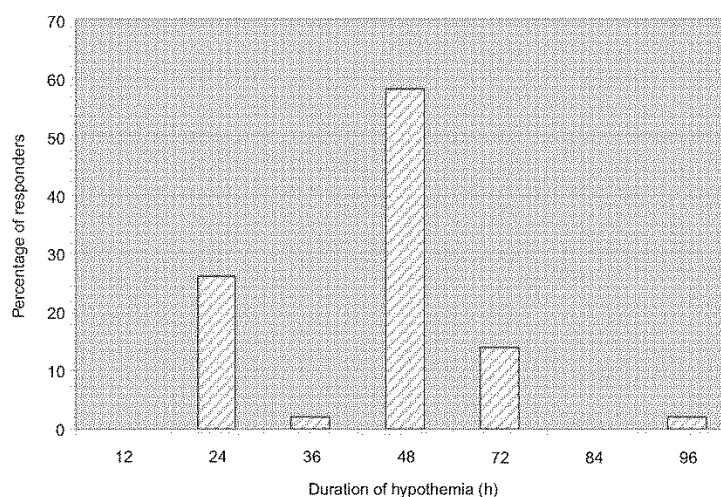


Figure 1 Maximum stated duration of therapeutic hypothermia used (n=65).

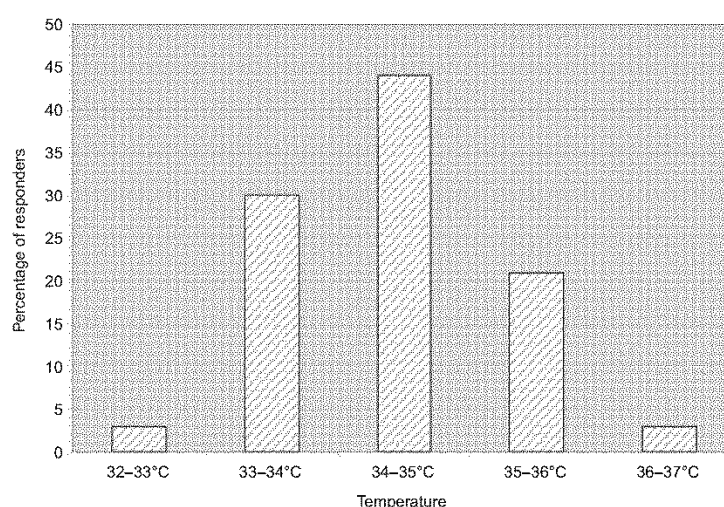


Figure 2 Target temperature for therapeutic hypothermia (n=77).

in children. A further study,⁶ supporting therapeutic hypothermia for neonates with hypoxic–ischaemic encephalopathy, was published after the survey was performed. It is conceivable that publication of this and other relevant studies could have an impact on clinicians' views and behaviour.

The recently commenced Therapeutic Hypothermia After Paediatric Cardiac Arrest (THAPCA) and Hypothermia after Cardiac Arrest in Paediatric (HypCAP) trials in North America and Canada will hopefully start to answer the question of safety and efficacy of this treatment in children. There is agreement (83%) that the results of these studies are likely to inform clinical practice in the UK, but support for a study also to be undertaken in the UK, which perhaps reflects that a number of trials showing an effect are required to change clinician's behaviour.

The use of deferred consent is a new area in paediatric resuscitation research in the UK. Recent changes in April 2008 to the Medicines for Human Use (Clinical Trials) Regulations, UK 2004 have allowed the use of deferred consent (with ethics committee approval) to be applied to emergency resuscitation research.¹⁴ In this survey 85% supported the use of deferred consent. The use of deferred consent may enable very earlier instigation of treatment during a clinical trial and therefore maximise the potential benefits of therapeutic hypothermia.

One of the strengths of this survey is the high response rate of 76%. A targeted approach to a defined population of UK PIC consultants with direct clinical involvement and decision making regarding patient care enable a degree of confidence that these findings reflect the current UK PIC community practice. As with all surveys however the findings only represent self-reported behaviour and do not necessarily equate to actual clinical behaviour. However, the findings give additional support for the need and willingness to undertake further investigative research into the use of therapeutic hypothermia after paediatric cardiac arrest.

Acknowledgements The authors are indebted to the paediatric intensive care consultants in the UK who took the time to complete this survey and Mr David Scholefield for the web-based support and survey design.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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9.8 Published paper: Survey of the use of therapeutic after cardiac arrest in UK paediatric emergency departments

Downloaded from emj.bmj.com on June 5, 2012 - Published by group.bmj.com

EMJ Online First, published on March 2, 2012 as 10.1136/emmermed-2011-200348

Original article

Survey of the use of therapeutic hypothermia after cardiac arrest in UK paediatric emergency departments

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► Additional material is published online only. To view this file please visit the journal online (http://emj.bmj.com/content/early/2012/03/02).

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Accepted 10 January 2012

ABSTRACT

Objectives To ascertain current use of therapeutic hypothermia (TH) after paediatric cardiac arrest in UK emergency departments (EDs), and views on participating in a UK randomised controlled trial (RCT) incorporating early induction of TH in ED.

Design Anonymous web-based survey of 77 UK Emergency Medicine (EM) consultants from 28 UK EDs that see children during the period April–June 2010.

Results 62% (48/77) of surveyed consultants responded from 21/28 (75%) EDs. All managed children post cardiac arrest, 90% (43/48) were aware of the literature concerning TH after cardiac arrest in adults. However, 63% (30/48) had never used TH in paediatric practice. All departments had at least one method of inducing TH (surface cooling; air/water blankets; intravenous cold fluid or catheters). Reasons stated for not inducing TH included no equipment available (26%; 11/42), TH not advocated by the local PICU (24%; 10/42) and not enough evidence for its use (24%; 10/42). TH was considered based on advice from the local Paediatric Intensive Care Units (68%; 17/25) or likelihood of recovery after arrest (32%; 8/25). There was strong support for a UK RCT of TH versus normothermia (85%; 40/47). The proposed RCT was felt to be ethical (87%; 40/46) with use of deferred consent acceptable (74%; 34/46).

Conclusion UK EM consultants are aware of TH but infrequently initiate the therapy in children for a number of reasons. Their involvement would enable early induction of TH in EDs after paediatric cardiac arrest during a UK RCT. The authors have demonstrated the availability of suitable equipment and EM consultant support for participation in such a RCT.

INTRODUCTION

Therapeutic hypothermia (TH) induced to 33±1°C has been shown to significantly improve neurological outcomes after ventricular fibrillation cardiac arrest in adults and hypoxic-ischaemic encephalopathy in neonates.^{1–5} Whether the same benefit would be achieved after paediatric cardiac arrest is not yet known, although the International Liaison Committee for Resuscitation (ILCOR) recommend 'considering the use of TH for 12–24 hours in infants and children who remain comatose after resuscitation'.⁶

Animal studies indicate that there is a narrow therapeutic window for TH, and early treatment appears more efficacious, especially in preventing more severe hypoxic-ischaemic injury after cardiac

arrest.^{7–10} Adult and neonatal studies showing neurological benefit have recruited patients to receive TH within 6 h of cardiac arrest or hypoxic injury.^{1–5} Whether the same therapeutic window applies to paediatric patients following cardiac arrest is as yet unknown.

Children who suffer out of hospital cardiac arrest are brought to their nearest emergency department (ED) for resuscitation. Following successful resuscitation, these patients are cared for in Paediatric Intensive Care Units (PICUs). With the centralisation of PICUs, these children often require transfer from the presenting ED to a regional PICU, often in a different hospital.¹¹ Due to logistical delays in transportation, it may be necessary for TH to be commenced in the referring ED in order to effectively deliver treatment in the postulated narrow therapeutic window.

The Cold-PACK (Post Arrest Cooling in Kids) study is a multi-centre randomised controlled trial (RCT) comparing TH with normothermia after paediatric cardiac arrest. It is currently in the protocol design stage, and its feasibility is being assessed in the UK. An important element of design is the ability to recruit patients and initiate treatment early after paediatric cardiac arrest. To achieve this, involvement of Emergency Medicine (EM) consultants working in EDs where children are resuscitated would be essential.

A previous survey of consultants in Paediatric Intensive Care in the UK identified a wide variation in uptake and use of TH at that time, but demonstrated support for a RCT of TH after paediatric cardiac arrest.¹² This survey of EM consultants aims to ascertain current practice regarding TH in UK EDs. In addition, it seeks to explore their attitudes and opinions, and assesses potential support from this group of physicians for the Cold-PACK study.

METHODS

Survey development

Relevant questions were generated by the study group and piloted on a group of eight EM consultants from three UK hospitals for further feedback and hyperlink access testing (see online supplementary material).

Survey execution

Seventy-seven EM consultants from 28 UK EDs were invited to participate. Half were from tertiary children's hospitals which have PICU on-site and see only children. The remainder were from secondary general hospitals which have no PICU on-site and

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see a mix of adults and children. For the purposes of this paper, we use the term EM consultants to refer to all consultants who participated in the survey. An invitation to participate was sent on the 1 April 2010. Invitations were sent three further times and the internet link was closed on the 30 June 2010.

Survey template

This was created using Microsoft ASPNET 2008 (Microsoft, Seattle, Washington, USA). Microsoft Excel (Microsoft) was used for data analysis and results are presented as a per cent of survey responders.

RESULTS

Of 77 EM consultants surveyed, 48 (62%) responded. Thirty-six (75%) were consultants solely in paediatric EM, and 12 (25%) held dual accreditation in adult and paediatric EM. Responses were from 21/28 (75%) EDs. Ten EDs were located in tertiary children's hospitals which only see children. Eleven were located in secondary general hospitals where consultants manage both adult and paediatric patients.

Consultants responded to questions about their current use of TH (table 1), how they select patients (table 2), methods of cooling available (table 3) and their views on further research (table 4).

Knowledge of the use of TH

In all, 90% (43/48) of consultants were aware of the literature regarding the use of TH in adults post cardiac arrest.

Very few used TH after paediatric cardiac arrest; 65% (30/46) reported use as 'never' and 30% (14/46) 'seldom'. No responder had a paediatric-specific TH protocol in his or her ED.

A larger proportion used TH after adult cardiac arrest; 27% (13/48) reported 'always' or 'often'. However, half answered 'not applicable' as they did not manage postcardiac arrest adults. Around 17% (8/46) reported being aware of an adult TH protocol in their ED.

The majority (89%; 42/47) did not know if TH improved outcome after paediatric cardiac arrest.

Patient selection

A number of variables were involved when deciding which patients should receive TH. There were also a number of reasons reported by clinicians for not using TH after cardiac arrest (table 2). Around 52% (25/48) responded to the 'reasons stated for selecting patients for TH post cardiac arrest in children'

Table 1 Use of TH

	n	Yes n (%)	No n (%)	Unknown n (%)		
Do you look after children post-cardiac arrest in ED?	48	48 (100)	0	0		
Are you aware of published research regarding TH in adults post-cardiac arrest?	48	43 (90)	5 (10)	0		
Do you have a TH protocol for adults?	46	8 (17)	25 (52)	13 (27)		
Do you have a TH protocol for children?	47	0	46 (98)	1 (2)		
Do you believe TH improves outcome after paediatric cardiac arrest?	47	5 (11)	0	42 (89)		
	n	Always	Often	Seldom	Never	NA
Do you use TH after adult cardiac arrest?	48	2 (4)	11 (23)	6 (13)	5 (10)	24 (50)
Do you use TH after paediatric cardiac arrest?	46	0	2 (4)	14 (30)	30 (65)	0

ED, emergency department; TH, therapeutic hypothermia.

Table 2 Selection of patients for TH

Factors stated in selecting patients for TH post paediatric cardiac arrest (n=25)	n (%)
On advice from PICU	17 (68)
Likelihood of patient recovery after the arrest	8 (32)
Absence of life limiting condition	6 (24)
Availability of equipment	6 (24)
Reasons stated for not using TH post paediatric cardiac arrest (n=42)	n (%)
No equipment available	11 (26)
Not enough research evidence	10 (24)
Not advocated by regional PICU	10 (24)
Not in the advanced paediatric life support guidelines	9 (21)
Rapid transfer to PICU where TH is usually started	6 (14)
Technically too difficult	6 (14)
Not considered for children	3 (7)
Not an emergency department priority or too infrequent	3 (7)
The cooling method available is too slow	2 (5)

PICU, Paediatric Intensive Care Unit; TH, therapeutic hypothermia.

question. The most frequent reason was 'on advice from the regional PICU'. Similarly, 24% (10/42) would not use TH as it was not advocated by the regional PICU and 14% (6/42) would transfer patients quickly to PICU and felt therapy could be commenced there with minimal delay rather than in the ED. The likelihood of patient recovery was also important for 32% (8/25) in choosing which patients should receive TH.

Methods of inducing hypothermia

Availability of equipment was reported as a factor in patient selection for TH and, conversely, lack of equipment was reported as a reason for not using TH (table 2).

A wide variety of equipment was available in EDs (table 3). ED availability was accepted if *any* consultant from an ED reported it available. Notably, there were discrepancies between responses from within the same ED regarding available equipment (mean inter-responder agreement score within each ED was 0.37; SD 0.06). About 86% of EDs had access to wet linen and 81% to ice packs. Cold air circulating blankets were reported to be present in 62% (13/21) of EDs although only 36% (15/42) of individuals reported it being available. There was a median of three methods of cooling (range 1–6) at each ED.

Opinions regarding future research into TH after paediatric cardiac arrest

A position of clinical equipoise is defined as the existence of an honest, professional disagreement among expert clinicians about the preferred treatment.¹⁵ Around 52% (24/46) of EM consultants agreed or strongly agreed that this exists regarding the use of TH after paediatric cardiac arrest. Only 7% (3/46) 'disagreed' and the remainder were neutral (table 4).

Table 3 Availability of methods for inducing therapeutic hypothermia reported by individuals and per emergency departments

Methods	Consultant response (n=42) n (%)*	Emergency department availability (n=21) n (%)*
Wet linen	35 (83)	18 (86)
Ice-pack to skin	24 (57)	17 (81)
Cold air blanket	15 (36)	13 (62)
Iced cold (4°C) intravenous saline	9 (21)	5 (24)
Cold water blanket	2 (5)	2 (10)
Intravascular cooling catheter	1 (2)	1 (5)

*Percentage total >100 as there was an option to select multiple methods.

Table 4 Opinions regarding therapeutic hypothermia randomised controlled trial

Please state your strength of agreement with the following:	n	Agreement* n (%)	Mean†	SD
There is clinical equipoise	46	24 (52)	3.5	0.69
It is ethical to perform a RCT	46	40 (87)	4.2	0.72
I approve of the use of deferred consent	46	34 (74)	3.8	1.10
Would you:	n	Yes n (%)	No n (%)	Don't know n (%)
Support a comparative intervention trial?	47	40 (85)	2 (4)	5 (11)
Support a method of cooling study?	45	34 (76)	5 (11)	6 (13)
Allow your patients to be recruited?	47	43 (91)	1 (2)	3 (6)
Use a trial protocol in your ED?	43	41 (95)	1 (2)	6 (13)

*Agreement = percentage responding 'agree' or 'strongly agree'.

†Mean score on a Likert scale: 5 (strongly agree), 4 (agree), 3 (neutral), 2 (disagree) and 1 (strongly disagree).

Ninety one per cent would agree to their patients being recruited into a RCT of TH after paediatric cardiac arrest. There was greater support for a trial of TH versus normothermia than there was for a method of cooling trial. There was strong support that a RCT of TH is ethical (87%) and that deferred consent is appropriate (74%).

DISCUSSION

The results of this survey suggest that very few UK EM consultants currently initiate TH after paediatric cardiac arrest in their ED. Various reasons for this emerge from the survey.

EM consultants are unsure whether TH improves outcome after paediatric cardiac arrest. There is an awareness of adult postventricular fibrillation cardiac arrest TH studies which have demonstrated a reduction in bad neurological outcome when treated with TH rather than normothermia.^{1,2,14} However, the vast majority of responding consultants in this survey did not know if TH improved neurological outcome after paediatric cardiac arrest.

The 2006 ILCOR guideline recommended the consideration of hypothermia therapy after paediatric cardiac arrest.⁶ A more recent edition of the ILCOR guideline has been published since this survey was carried out. However, the recommendations have changed only for adolescents, suggesting that TH is beneficial after ventricular fibrillation cardiac arrest in this group.¹⁵ The evidence to support the ILCOR recommendation is from animal, neonatal and the adult studies described above. There has been no paediatric-specific RCT. Only two retrospective observational cohort studies^{16,17} have been published in this area, but they use unbalanced groups and show no difference in outcomes of patients receiving TH compared with normothermia. This lack of evidence may explain the demonstrated lack of uptake of this recommendation. The ongoing Therapeutic Hypothermia After Paediatric Cardiac Arrest multi-centre RCT (clinical trial.gov ID: NCT00880087 and NCT00878644) in the USA may gather important data on safety and efficacy to strengthen any future guidance.

The role of the regional paediatric intensive care team appears to influence the management of paediatric postcardiac arrest patients in the ED. Of EM consultants who would consider using the therapy, 68% reported that they would only commence it if their regional PICU requested and advocated it. If the time taken to admit to PICU was anticipated to be short, then therapy would be delayed until then.

A number of methods of cooling appear to be accessible in most EDs. However, between consultants from the same ED, there is discrepancy in the perception of what equipment is available. There was a belief that the PICU would have access to more sophisticated cooling equipment and be able to

administer the therapy more safely. This may be due to lack of personal experience and infrequent use of the equipment. Three members of this group have previously reported the results of a survey of UK Paediatric Intensive Care consultants conducted in 2009.¹² In this survey, 48% (66/113) of responders 'always' or 'often' used TH after paediatric cardiac arrest. Of those who had used TH, only 30% (24/73) would actively induce TH in an ED. The regional variation of paediatric intensive care practice and the low proportion who would consider starting the therapy in the ED mirror the findings in this present study.

Further points

This survey highlights the lack of existing protocols for the management of paediatric postcardiac arrest temperature. The temperature of paediatric patients transferred to PICU after cardiac arrest tends already to be low. The US study by Fink *et al* reported a mean postcardiac arrest PICU admission temperature of 34.6°C (±2.2). This included all patients admitted irrespective of whether they were subsequently treated with TH or normothermia.¹⁶ Data for postcardiac arrest temperature of UK children in the ED or PICU are not yet available. However, we hypothesise that young infants and toddlers would generally reduce their core temperature or become frankly hypothermic during or after a cardiac arrest due to the exposure necessary for effective resuscitation despite all efforts to maintain normothermia. Complex methods of inducing TH may therefore not be required in the initial stages. Larger children and adolescents may require more active therapies to initiate and maintain hypothermia or normothermia. Simple methods such as intravenous iced cold (4°C) saline have been used successfully in adults^{18–20} and children^{21,22} and should be easily accessible with minimal resource implications. Alternatively, if available, more complex methods such as servo-controlled surface cooling air or water blankets could be used.²³ However, continuous monitoring of core temperature (rectal, oesophageal or bladder) would be essential in all cases. Further research is needed to enable the development of consensus guidelines on appropriate paediatric temperature monitoring and management.^{24,25}

Only 52% of EM consultants agreed that there is clinical equipoise regarding the use of TH after paediatric cardiac arrest, although another 41% were 'neutral'. The presence of clinical equipoise remains a fundamental prerequisite to undertaking a RCT.¹⁰ There is strong support among EM consultants (85%) for a comparative trial of TH versus normothermia in paediatric patients post cardiac arrest. A large proportion (91%) of these consultants would allow their patients to be recruited into such a study.

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The use of deferred consent is still a relatively new process in paediatric resuscitation research in the UK. Changes were made to the Medicines for Human Use (clinical trials) regulations UK in 2008, allowing deferred consent to be used (with ethics committee approval) in emergency resuscitation research.³⁶ Approval for the use of deferred consent as demonstrated in this survey (74%) would allow very early patient recruitment and initiation of temperature control. This would maximise the potential benefits of TH by ensuring the desired temperature is reached within the postulated narrow therapeutic window.

Limitations

This survey targeted EM consultants with direct clinical involvement and decision-making responsibility for paediatric patients. We achieved a credible 62% response rate, but not all UK EM consultants, some of whom may occasionally manage paediatric cardiac arrest patients, were surveyed. In addition, as with all surveys, the findings only represent self-reported behaviour and do not necessarily equate to actual clinical behaviour. However, the findings of this survey add strength to the case for further investigative research into the use of TH after paediatric cardiac arrest. We have demonstrated both additional support for, and willingness to participate, in such a RCT, which would incorporate early use of TH in the ED.

CONCLUSION

This survey of practice and opinions finds that very few UK EM consultants initiate TH in their EDs after paediatric cardiac arrest. Regional PICUs play significant roles in influencing the management of paediatric cardiac arrest patients. With their support, EM consultants would consider using TH. Although simple methods of cooling patients are already available in most EDs, their use is limited due to clinician concerns regarding safety, lack of protocols and lack of evidence of improved outcomes. There is support among UK paediatric intensive care and EM consultants for further research into the safety and efficacy of TH. This research would require involvement of EM consultants and their departments in order to be able to initiate TH early. This survey supports the proposal that the feasibility of the Cold-PACK Study of TH versus normothermia commenced in the ED after paediatric cardiac arrest should be explored further.

Acknowledgements We are indebted to the paediatric emergency medicine consultants in the UK who took the time to pilot and complete this survey and we thank Mr David Scholefield for the web-based support and design.

Contributors BS and ML designed data collection tools, monitored data collection and analysed the data. BS drafted and revised the paper. BS is guarantor. ML revised the paper. KB, HD and KM piloted data collection tool, analysed the data and revised the paper. DS adapted the data collection tool for internet use.

Competing interests None.

Ethics approval This study was a service evaluation via a survey of medical practitioners working in emergency medicine in the UK; we, therefore, were satisfied that ethics committee approval was not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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9.9 Chronic condition coding

Table 9-1 Chapter five: Chronic condition groupings and subgroups for epidemiological study

Chronic Condition Groups	Subgroups	Chronic Condition Groups	Subgroups
Respiratory	Asthma	Cardiac	Endocarditis/Myocarditis
	Pulmonary Hypertension		Cardiomyopathy
	Congenital Anomaly (e.g. Tracheo-oesophageal fistula/Congenital diaphragmatic hernia)		Simple Cardiac: (Ventricular septal defect /Atrial septal defect /Coarctation/ Patent ductus arteriosus/ Aortic or pulmonary stenosis)
	Upper airway obstruction (including Cleft palate)		Complex cardiac (single ventricle/TAPVD/LCAPA/TG A/TOF/AVSD)
	Chronic Respiratory Disorder (e.g. Cystic Fibrosis)		Rhythm disorder (e.g. prolonged QT syndrome)
	Chronic Lung Disease		Cardiac Syndrome (Marfan's)
	Tracheostomy		Heart transplant
	Other		Other
	Brain Malformation	Liver	Any chronic liver disorder
	Brain Tumour	Haematological	Any haematological condition
Neurological	Cerebrovascular event or anomalies	Oncological	Solid tumour
	Central nervous system Infection (e.g. meningitis)		Non-solid tumour
	Convulsions		Bone marrow transplant
	Genetic syndrome	Metabolic or endocrine	Any metabolic disorder
	Hydrocephalus		Born < 28 weeks gestation
	Neuromuscular	Prematurity	Born ≥ 28 and <32weeks gestation
	Spinal anomalies		Born ≥ 32 and <36weeks gestation
	Neonatal hypoxic ischaemic encephalopathy	Gastrointestinal	Necrotising enterocolitis
	Brain Trauma (Non-accidental/accidental)		Other
	Intraventricular bleed (non-trauma)	Renal	Any chronic renal disorder
	Myasthenia gravis	Genetic	Genetic syndrome (e.g. Trisomy 21: Down's)
	Chronic Degenerative (e.g. Leigh's Leucodystrophy)		Any immunodeficiency syndrome
	Other	Other (relevant)	Other significant chronic condition

9.10 Conference abstract

CARDIAC ARREST REQUIRING INTENSIVE CARE ADMISSION: A UNITED KINGDOM EPIDEMIOLOGY STUDY.

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Objectives: To describe the epidemiology of children (0-18yrs) admitted to UK paediatric intensive care units (PICUs) after in-hospital (IHCA) and out-of-hospital cardiac arrest (OHCA). To inform the design of a UK post-cardiac arrest intervention trial (The Cold-PACK Study: Post Arrest Cooling in Kids).

Methods: Extraction and analysis of IHCA and OHCA admissions from the prospectively collected national PICANet Database containing information on admissions to 30 PICUs in the UK and Eire between January 2003 and June 2010.

Results: 1703 children were admitted to PICU following cardiac arrest (51% IHCA, 49% OHCA). OHCA admission to PICU overall population incidence rate was 1.3 per 100'000 children per year (patients <1yr of age incidence rate = 8.9). IHCA and OHCA each accounted for 0.8% (IQR 0.6–1.0) of all PICU admissions. Median age of IHCA was significantly lower. Preceding chronic conditions were more common in IHCA (79%) than OHCA patients (48%). 74% of OHCA were admitted from other hospitals requiring retrieval to PICU compared to 41% of IHCA. 17% of OHCA cases were trauma related of which 65 (8%) were near-drowning and 28 (3%) hanging. Pupils were fixed and dilated in 22% of OHCA admissions with a 96% PICU mortality. PICU survival was significantly higher for IHCA patients (76% versus 50%; $p < 0.01$).

Conclusions: The UK rates of survival from PICUs after IHCA and OHCA appear higher than previously reported. There is a high proportion with preceding chronic conditions and important UK population incidence rates are available to guide trial feasibility in the UK.

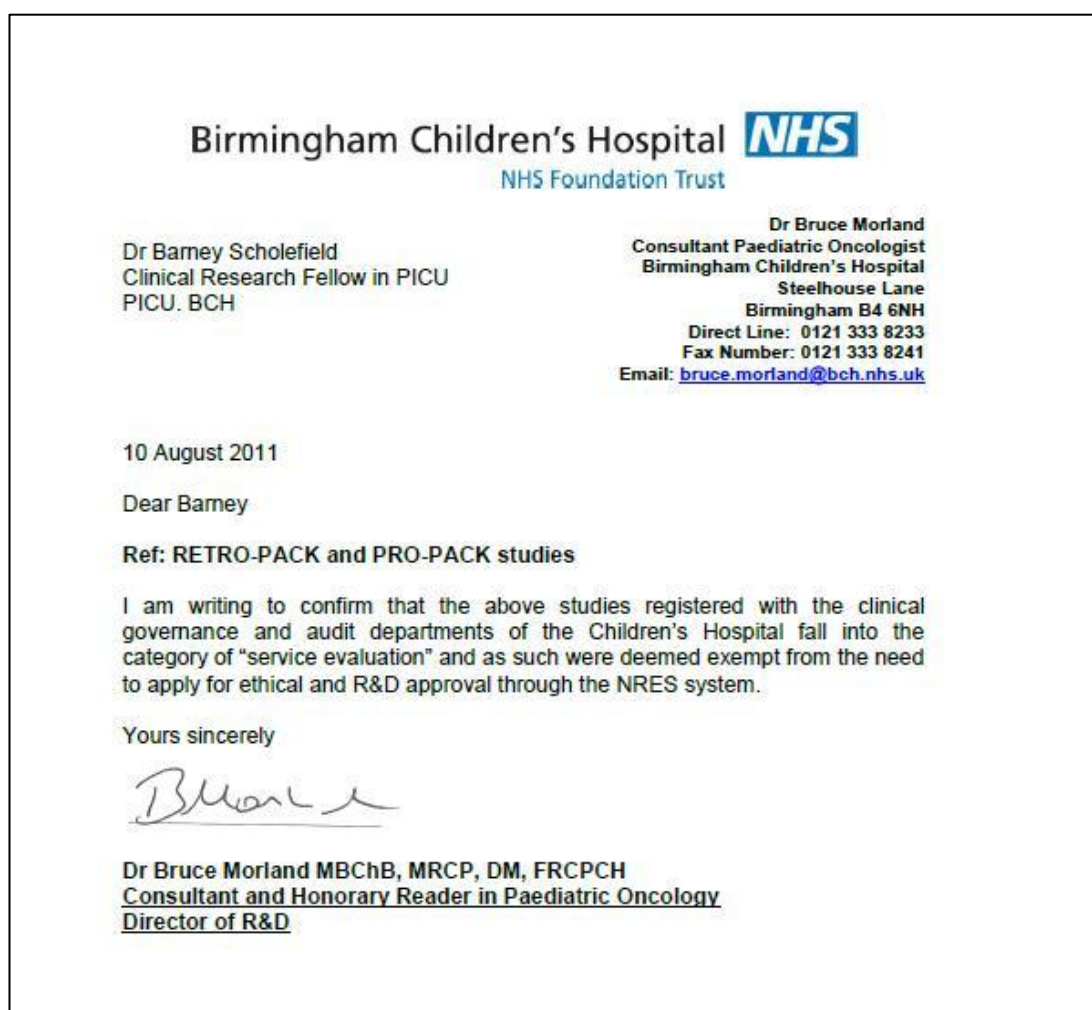
Table 1 Patient Characteristics

	IHCA (n= 862)	OHCA (n = 841)	p value
Age (yrs)*	0.6 (0.2 – 3.0)	1.1 (0.2 – 7.8)	< .001
Male gender %	56%	58%	ns
Probability of death on admission (PIM2)*	0.25 (0.13 – 0.46)	0.38 (0.21-0.73)	<.001
Length of PICU stay*	6.0 (2.0-12.0)	4.0 (2.0-8.0)	<.001
Length of ventilation*	5.0 (2.0-10.0)	4.0 (2.0-7.0)	<.001
Chronic Condition (%)	677 (79%)	401 (48%)	<.001
Fixed and dilated pupils on admission (%)	43 (5%)	191 (22%)	<.001
Survival rate to PICU discharge	653 (76%)	418 (50%)	<.001

*median (IQR)

9.11 Letter of support from Birmingham Children's Hospital director of research and development

Letter of support for the RETRO-PACK (RETROspective Post Arrest Cooling in Kids) studies which are presented in Chapters 6 & 7. Please note the shortened term for the studies has not been presented in this thesis. The PRO-PACK study is a follow-on study which does not form part of this thesis.



10 References

*“Before beginning a Hunt, it is wise to ask someone what you are looking for
before you begin looking for it.”*

*In: Winnie the Pooh, Pooh's Little Instruction Book
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